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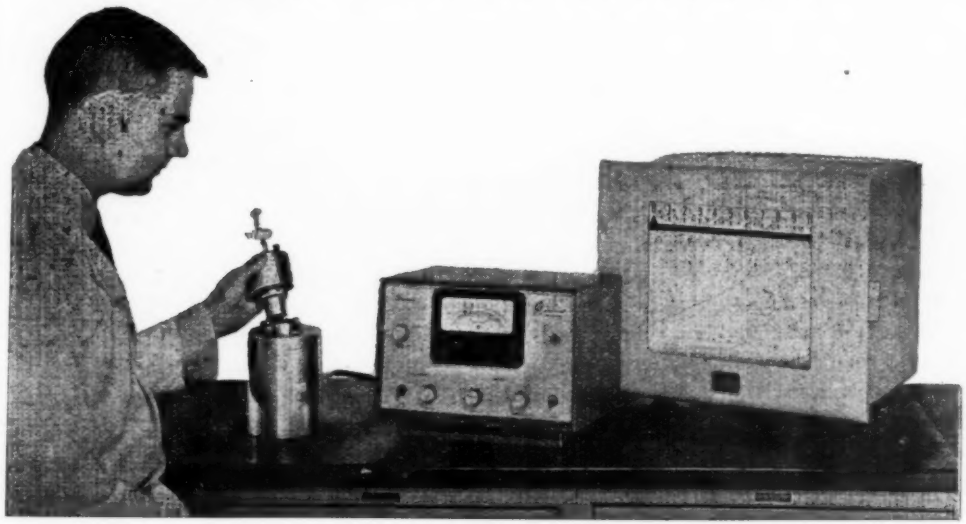

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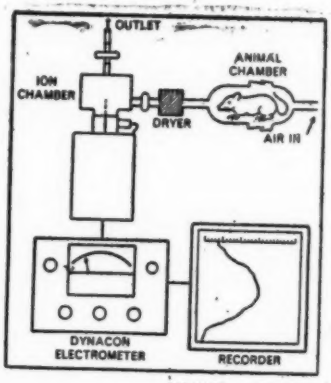


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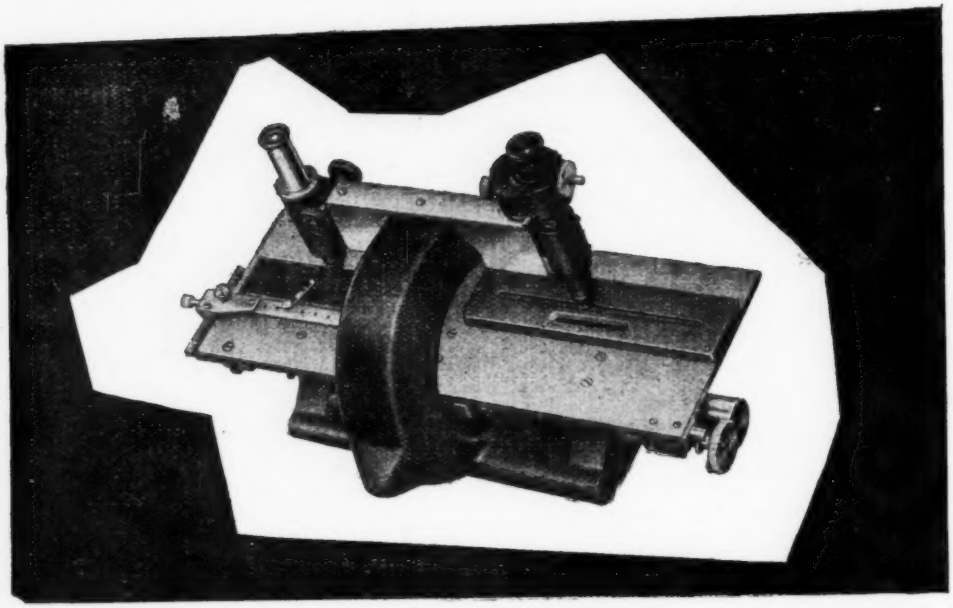

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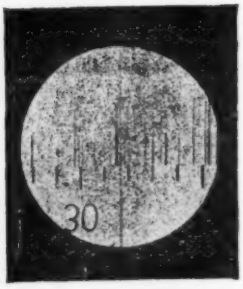


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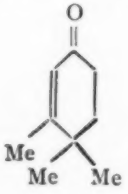
[Jour. Indian Chem. Soc., Vol. 36, No. 5, 1958]

# TERPENOIDS. PART V. SYNTHESIS OF 4 : 4 : 3-TRIMETHYL*cyclo*HEX-2-ENONE

By R. P. Gandhi, Baldev Vig and S. M. Mukherji

An unambiguous synthesis of 4 : 4 : 3-trimethyl*cyclo*hex-2-enone, the principal component of "Tiemann's *iso*camphorphorone" has been described.

Consequent upon the reported oxidative transformation of β-campholenic acid to the six-membered unsaturated ketone (I) by Tiemann (*Ber.*, 1897, **30**, 342 ; 1895, **28**, 2167), an interpretation of the mode of this cyclic artifact and its synthetic production were studied by several workers (Bouveault, *Bull. soc. chim.*, 1898, *iii*, **19**, 565 ; Buchman and Sargent, *J. Org. Chem.*, 1942, **7**, 140 ; Von Braun *et al.*, *Annalen*, 1931, **490**, 188 ; *Chem Abst.*, 1932, **26**, 427). It was demonstrated (Buchman and Sargent, *loc. cit.*) that the original "Tiemann's *iso*camphorphorone" preparation was a mixture of the ketones (I) and (II) with the former constituting the principal component. The synthetic preparation of αβ-pulenenone (II) was earlier described by Auwers and Hassenland (*Ber.*, 1908, **41**, 1812). However, the preparation of the predominant ketonic isomer (I) has so far been restricted only to the adaptation of Tiemann's original fortuitous method or to the modified oxidation reaction with lead tetra-acetate on dihydroxydihydro-β-campholenic acid, proved to be an intermediate in the Tiemann's preparation of (I) (Buchman and Sargent, *loc. cit.*). This course, involving, as it does, a single or two-stage conversion of dihydroxydihydro-β-campholenic acid or β-campholenic acid into the six-membered cyclic ketone (I) through an assumed intermediate keto-acid, remains equivocal in so far as it admits of the simultaneous formation of the alternate structure (II) (cf. Buchman and Sargent, *loc. cit.*).




(I)

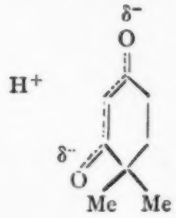
(II)

In view of this and of the utility of the ketone (I) in synthetic work (cf Buchman and Sargent, *loc. cit.*), a new and straightforward synthetic route to (I) has now been worked out. Our approach envisages the conversion of an appropriately substituted *cyclo*hexan-1 : 3-dione into its enolic ether (Frank and Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645) which serves as a precursor of αβ-unsaturated cyclic ketones (cf. Seifert and Schinz, *Helv. Chim. Acta*, 1951, **34**, 728 ; Gandhi, Walia and Mukherji, this *Journal*, 1957, **34**, 509).

The diketone (III ; Ensor and Wilson, *J. Chem. Soc.*, 1956, 4068) was prepared in an improved yield (vide Experimental), starting from diethyl αα-dimethylglutarate. An essentially identical procedure to that of the Ensor and Wilson method was followed with the difference that these authors used the corresponding dimethylglutarate as the starting material and sodium methoxide for cyclisation.

(III)

(IV)




(V)

The diketone (III), on treatment with butanol$^t$ in refluxing benzene in the presence of catalytic amount of PTS, was converted, in 62.2% yield, into 6:6-dimethyl-3-butoxy$^t$ *cyclo*hex-2-enone (IV). The orientation in the enolic ether (IV) is based on the considerations of stereo-interactions involving the geminal dimethyl and the butoxy$^t$ groups. Moreover, if the mesomeric enolate ion (V) is the intermediate in the formation of the enolic ether (IV), the charge density should be the most on the oxygen atom furthest from the butyl$^t$ moiety having strong electron-repelling inductive effect (+ I effect).

The enol ether (IV) was then allowed to react with methylmagnesium iodide and the intermediary carbinol (not isolated), on subsequent acid treatment, underwent smooth conversion into 4:4:3-trimethyl*cyclo*hex-2-enone (I) in 72% yield. No trace of αβ-pulenenone (II) could be detected in the final product (I), thus showing the unidirectional enolic ether fromation as in (IV). The αβ-unsaturated ketone (I) furnished a semicarbazone and a deep red 2:4-dinitrophenylhydrazone.

## *Experimental

*Diethyl αα-Dimethylglutarate.*—αα-Dimethylglutaric acid was obtained from γ-formylcapro$^t$-nitrile (Born *et al.*, *J. Chem. Soc.*, 1953, 1781) through a hydrolysis-oxidation sequence (Lewis and Hinds, *J. Amer. Chem. Soc.*, 1952, **74**, 304) and finally converted into the corresponding di-ester.

*Ethyl hydrogen-αα-dimethyl glutarate* was prepared from the preceding ester (80 g.), KOH (20.7 g.) and ethanol (200 c.c.) in 85% yield (60 g.), b.p. 155-60°/6 mm. (Found : C, 57.35 ; H, 8.70. $C_9H_{16}O_4$ requires C, 57.43 ; H, 8.57%).

*γ-Ethoxycarbonyl-γγ-dimethylbutyryl Chloride.*—A mixture of the acid-ester (60 g.), anhydrous benzene (100 c.c.) and thionyl chloride (50 g.) yielded 55 g. (83.46%) of the ester-acid chloride, b.p. 112-15°/5 mm. (Found : C, 52.60 ; H, 7.35. $C_9H_{15}O_3Cl$ requires C, 52.17 ; H, 7.20%).

* Melting and boiling points are uncorrected. Microanalyses by Drs. Weiler and Strauss, Oxford.

*Ethyl δ-Keto-αα dimethylcaproate.*—Cadmiumdimethyl, prepared from anhydrous cadmium chloride (46.5 g.) and MeMgI (from 78 g. MeI), when allowed to react with the above acid chloride (51.6 g.) in benzene at reflux temperature for 1/2 hour, produced 26 g. (55%) of the corresponding keto-ester, b.p. 112°/7 mm. (Found: C, 63.96; H, 9.60. $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74%).

4:4-*Dimethylcyclohexan*-1:3-*dione* (III).—To a suspension of dry potassium butoxide[4] (from 3.9 g., 0.1 g. atom of K) in anhydrous ether (100 c. c.) was introduced. gradually and with cooling, ethyl δ-keto-αα-dimethylcaproate (20 g., 0.1*M*) in dry ether (30 c.c.). The contents were then left standing at room temperature for 12 hours and finally refluxed for 1½ hours. The reaction mixture was decomposed with ice-cold HCl (dil., 80 c.c.). On working up the hydrolysate in the customary manner, a highly viscous colorless oil (12 g., 79%) was obtained, b.p. 130°/7 mm, which solidified on keeping. Crystallised from benzene-pet. ether mixture (60-80°) as colorless needles, it melted at 106° (lit. m.p. 103-105°).

The diketone did not exhibit any characteristic colour with alcoholic ferric chloride solution. (Found: C, 69.1; H, 8.35. $C_8H_{12}O_2$ requires C, 68.54; H, 8.63%).

6:6-*Dimethyl*-3-*butoxy*[4]*cyclohex*-2-*enone* (IV).—A mixture of diketone (VII, 12 g., 0.857*M*), butanol[4] (8 g., 0.1*M*), anhydrous benzene (100 c.c.) and a little *p*-toluenesulphonic acid was refluxed under a Dean and Stark water-separator for about 6 hours (when water stopped collecting in the separator). Thereafter, the contents were cooled and excess PTS was destroyed with a little sodium ethoxide in ethanol. Water (100 c.c.) was added and the organic material was taken up in ether. After removal of the solvent the residue was distilled in vacuum to obtain 10 g. (62.2%) of a colorless oil, b.p. 115°/3 mm, $n_D^{32}$ 1.463. (Found: C, 72.92; H, 10.2. $C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27%).

4:4:3-*Trimethylcyclohex*-2-*enone* (I).—Grignard reagent was prepared from clear dry magnesium (1.8 g., 0.075 g. atom), MeI (11 g., 0.08*M*) and dry ether (50 c.c.). To this was added *iso*butoxyketone derivative (IV) (10 g., 0.05*M*) dropwise and under ice-cooling. The contents were left overnight and then refluxed for an hour. The reaction mixture was decomposed with $H_2SO_4$ (cold, dilute, 50 c.c.) and the hydrolysate, after having been stirred at 0-10° for 4-5 hours, was worked up in the usual way to obtain 5 g. (71.4%) of a colorless oil, b.p. 93-95°/10 mm, $n_D^{24}$ 1.4840. (Found: C, 78.23; H, 10.6. $C_9H_{14}O$ requires C, 78.21; H, 10.21%).

The 2:4-*dinitrophenylhydrazone* of the ketone was prepared in the usual manner which, after crystallisation from absolute ethanol, afforded deep red needles, m.p. 168°. (Found: N, 17.3. $C_{15}H_{18}O_4N_4$ requires N, 17.60%).

The *semicarbazone* on crystallisation from ethanol was obtained as colorless needles, m.p. 206-207° (lit. m. p. 206.5-207°; Buchman and Sargent, *loc. cit.*). (Found: N, 21.8. $C_{10}H_{17}ON_3$ requires N, 21.52%).

CHEMISTRY DEPARTMENT,
PANJAB UNIVERSITY,
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# ESTIMATION OF NICKEL BY αβ-DIOXIMINOACETOACETANILIDE

By J. S. Dave and A. M. Talati

αβ-Dioximinoacetoacetanilide precipitates nickel quantitatively as $Ni(C_{10}H_{10}O_3N_3)_2$ at *p*H 6.2-8.6. Effect of ions on the estimation of nickel by this reagent has been investigated.

α-Dioximes have found wide applications in the detection and estimation of nickel. Thus, dimethylglyoxime (Tschugaeff, *Z. anorg. Chem.*, 1905, **46**, 144), α-benzildioxime (Atack, *Analyst*, 1913, **38**, 316), diphenylglyoxime (Gutzeit, *Helv. Chim. Acta*, 1929, **12**, 829, 841), 1 : 2-*cyclo*hexanedione dioxime (Wallach, *Annalen*, 1914, **437**, 148; Voter *et al.*, *Anal. Chem.*, 1948, **20**, 458), etc. are suggested as reagents for nickel. In the present communication the investigations on the use of αβ-dioximinoacetoacetanilide as a reagent for nickel have been discussed. Nickel forms with αβ-dioximinoacetanilide an organge-yellow complex which is formulated as $Ni(C_{10}H_{10}O_3N_3)_2$. Nickel is quantitatively precipitated by this reagent within the *p*H range 6.2-8.6. Various anions and cations (studied herein) do not interfere with the estimation of nickel by this reagent under prescribed conditions.

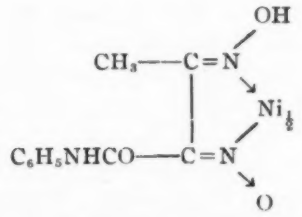
## Experimental

αβ-Dioximinoacetoacetanilide was prepared from acetoacetanilide (Dave and Talati, *Curr. Sci.*, 1957, **26**, 326). 1% Alcoholic solution of this reagent was used for all estimations.

A weighed quantity of nickel chloride (Analar) was dissolved in a little water and diluted to a definite volume. Nickel content of the solution was determined by the dimethylglyoxime method. All other reagents used were of C.P. grade.

*Preparation and Composition of the Complex.*—Nickel chloride solution (10 c.c.) was diluted to about 100 c.c. with distilled water and to the warm solution was added a sufficient amount of the reagent solution. An orange-yellow precipitate was obtained which was digested on the water-bath for about an hour. The precipitates were filtered, washed with water and alcohol and dried at 110-20°. A weighed quantity of the precipitate was digested with aqua regia to oxidise the organic matter, and then evaporated nearly to dryness in presence of excess HCl. The residue was extracted with HCl (dil.) and its nickel content was determined by the dimethylglyoxime (DMG) method. [Found: Ni (by DMG), 11.71, 11.74. Calc. for $Ni(C_{10}H_{10}O_3N_3)_2$: Ni, 11.76%].

The results suggest the composition as $Ni(C_{10}H_{10}O_3N_3)_2$ for the nickel complex of αβ-dioximinoacetoacetanilide, which may be represented as



*Analytical Procedure.*—An aliquot quantity of nickel chloride solution was diluted to about 200 c.c. with distilled water, warmed and to it was added a sufficient amount of the reagent solution (1 g. reagent for 0.09 g. Ni and the *p*H was adjusted to 7.0 to 8.0. The orange-yellow precipitate formed was digested on the water-bath for about an hour, filtered through a sintered glass crucible or quantitative filter paper, washed with water and dried at 110-20° to a constant weight. This was weighed as $Ni(C_{10}H_{10}O_3N_3)_2$, the factor for nickel being 0.1176. Some of the results are recorded in Table I.

TABLE I

| Ni taken. | Salt added. | | Ni-chelate obtained. | Ni found. | Error. |
|---|---|---|---|---|---|
| 5.81 mg. | ... | ... | 57.8 mg. | 6.80 mg. | −0.01 mg. |
| 13.22 | ... | ... | 112.6 | 13.24 | +0.02 |
| 20.03 | ... | ... | 170.9 | 20.10 | +0.07 |
| 26.44 | ... | ... | 224.4 | 26.39 | −0.05 |
| 13.22 | Na-Ac | 2.0 g. | 112.1 | 13.18 | −0.04 |
| 6.81 | $K_2SO_4$ | 2.0 | 58.2 | 6.84 | +0.03 |
| 6.81 | KBr | 2.0 | 57.9 | 6.81 | ±0.00 |
| 6.81 | KI | 2.0 | 58.2 | 6 84 | +0.03 |
| 13.22 | $CdSO_4$ | 0.064 | 113.2 | 13.31 | +0.09 |
| 6.81 | $FeCl_3$ | 0.338 | 57.3 | 6.74 | −0.07 |
| 6.81 | $CaCl_2$ | 0.55 | 58.1 | 6.83 | +0.02 |
| 6.81 | $BaCl_2$ | 0.75 | 57.8 | 6.80 | −0.01 |
| 6.81 | $MgCl_2$ | 0.50 | 58.4 | 6.87 | +0.06 |
| 13.22 | $HgCl_2$ | 0.068 | 113.4 | 13.33 | +0.11 |
| 6.81 | $CrCl_3$ | 0.033 | 57.8 | 6.80 | −0.01 |
| 13.22 | $ZnSO_4$ | 0.072 | 111.3 | 13.09 | −0.13 |

*Effect of* *p*H.—In order to study the *p*H range over which nickel could be completely precipitated by these reagents, estimation of nickel was carried out in solutions having different *p*H values. *p*H of the undiluted filtrates was determined by L and N *p*H meter. The results recorded in Table II show that nickel is completely precipitated by this reagent within *p*H 6.2-8.6.

TABLE II

| Ni taken. | *p*H. | Ni-chelate obtained. | Ni found. |
|---|---|---|---|
| 13.22 mg. | 5.02 | 108.4 mg. | 12.75 mg. |
| 6.81 | 5.42 | 55.5 | 6.53 |
| 6.81 | 6.22 | 57.7 | 6.79 |
| 6.81 | 6.94 | 57.8 | 6.80 |
| 6.81 | 8.58 | 57.9 | 6.81 |
| 13.22 | 9.62 | 90.5 | 10.64 |

*Effect of Anions and Cations.*—In order to study the effect of ions, estimation of nickel was carried out in presence of different anions and cations at *p*H 7-8. (In presence of tervalent cations like $Cr^{3+}$ and $Fe^{3+}$, estimations were carried out after complexing these ions with citric or tartaric acid). The results are recorded in Table I.

The results indicate that in presence of ions like bromide, iodide, sulphate, mercuric, cadmium, ferric, chromium, zinc, calcium, barium, magnesium, the estimation of nickel by this reagent is satisfactory.

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CHEMISTRY DEPARTMENT,
FACULTY OF SCIENCE,
AND
TEXTILE CHEMISTRY DEPARTMENT,
FACULTY OF TECHNOLOGY AND ENGINEERING,
M. S. UNIVERSITY OF BARODA, BARODA.

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# VISUAL TITRATIONS IN NON-AQUEOUS SOLVENTS WITH CRYSTAL VIOLET AS AN INTERNAL INDICATOR

By Ram Chand Paul, Jaswant Singh and Sarjit Singh Sandhu

Acid-base titrations in solvents, such as phosphorus oxychloride, thionyl chloride, arsenic trichloride, carbon tetrachloride and chlorobenzene, have been attemped with crystal violet as an internal indicator. The reversible nature of the indicator with stannic chloride and titanium tetrachloride as acids, and quinoline, α-picoline and dimethylaniline as bases in phosphorus oxychloride and thionyl chloride has been indicated. In the case of arsenic trichloride, the basic solutions are only successfully used as titrants. Carbon tetrachloride and chlorobenzene do not allow the quantitative assessment of the acids and bases in these titrations as the reaction is very slow and the indicator is usually irreversibly adsorbed by the precipitate formed during the titration or is chemically attacked. A marked difference in the mode of the reaction of these acids and bases in polar and non-polar solvents is suggested.

The colour changes of an acid-base indicator usually depend upon the *p*H or the concentration of $H^+$ and $OH^-$ ions in aqueous solutions. Quite recently, the study of solvents, such as phosphoryl chloride and arsenic trichloride (Gutmann, *Monatsh.*, 1954, **85**, 393 ; 1952, **83**, 159 ; 1953, **84**, 1191 ; Anderson and Lindqvist, *Acta Chem. Scand.*, 1955, **9**, 79) has shown that these also ionise like water. In these solvents, however, the acids and bases would be those substances which would increase the concentration of cations or anions characteristic of the solvents. In case the proposed ionic species actually exist, it should be possible to study a change in their concentration with the help of indicator dyes. But these solvents appear to attack the compounds which contain hydroxyl and primary or secondary amino groups.

Crystal violet, which possesses tertiary amino groups, seems to work satisfactorily. It has already been used as an indicator in thionyl chloride (Garber *et al.*, *Anal. Chem.*, 1953, **25**, 581) though not with much success. However, its use has recently been extended to acid-base titrations in acetyl chloride (Paul *et al.* *Chem. & Ind.*, 1958, 622 ; Singh *et al.*, *J. Chem. Soc.*, 1959, 845) and benzoyl chloride (Paul *et al.*, this *Journal*, 1958, **35**, 877). Encouraged by the successful working of this indicator in the aforementioned solvents, which are clearly similar to phosphoryl chloride, thionyl chloride and arsenic trichloride, acid-base titrations with the aid of this indicator have been carried out in these solvents. The difference between the influence of the nature of ionising and non-ionising solvents has also been studied, and the results obtained in chlorobenzene and carbon tetrachloride are not sufficient for quantitative interpretation. The present investigation comprises the study of neutralisation reactions between the Lewis acids-stannic chloride and titanic chloride, and the organic tertiary bases-pyridine, α-picoline, quinoline and dimethylaniline.

## EXPERIMENTAL

Phosphorus oxychloride (commercial) was fractionated in an all-glass apparatus and the fraction boiling at 104-105° was collected. The distillate was mixed with 10% dimethylaniline (by weight) to remove acidic impurities, and refractionated to obtain a colorless distillate boiling at 106°/740 mm.

Thionyl chloride was purified by treating the distillate (b.p. 74-76°), obtained from the commercial sample, with 2% quinoline and the fraction boiling at 75.5°/732 mm was collected. Arsenic trichloride was fractionated and the distillate boiling between 129° and 131° was treated with 10% dimethylaniline. The mixture was refractionated when arsenic trichloride boiling at 130°/732 mm was taken.

Stannic chloride and titanium tetrachloride were kept over tin (A.R.) pieces and copper turnings respectively and fractionally distilled in an all-glass apparatus in an atmosphere of dry nitrogen. $TiCl_4$, b. p. 130-31°/740 mm ; $SnCl_4$, b. p. 112.5-13°/712 mm.

Organic tertiary bases-pyridine, α-picoline and dimethylaniline, were purified by usual methods and fractionally distilled. Quinoline was first precipitated as zinc chloride complex which was decomposed with alkali, quinoline extracted with ether and finally fractionated. Quinoline, b.p. 229-30°/740 mm ; pyridine, b.p. 112-12 5°/737 mm ; α-picoline, b.p. 126-26.5°/735 mm ; dimethylaniline, b.p. 192-93°/735 mm.

Chlorobenzene and $CCl_4$ were purified by usual methods and dried over $P_2O_5$. The liquids were fractionally distilled. Chlorobenzene, 131°/739 mm ; $CCl_4$, 76°/740 mm.

*Procedure.*—In the manipulation of solutions a dry box was employed and while weighing the substance, maximum care was taken to avoid the contact of moist air. The titration assembly consisted of a modified microburette equipped with a reservoir for storing the titrant solution and the nozzle of the burette was fixed inside a titration bottle through an impregnated cork. The substance to be titrated was weighed by difference and added directly to the titration bottle containing 20 c.c. of the solvent. Thereafter crystal violet (approximately 5 mg.) was added and the reaction mixture was agitated by means of a magnetic stirrer to produce a coloured solution. After this, the addition of the titrant was commenced dropwise and the reaction mixture was continually stirred. When a perceptible change in the colour of the indicator was observed, the stirring of the solution was stopped so as to allow the precipitate to settle down, and the colour of the supernatant layer was noted. The colour change of the indicator, close to the calculated end-point, was considered for computing the volume used at the end-point. The formation of a precipitate usually resulted in every titration and the precipitate took a long time to settle down, as otherwise, the colour change could not be observed with precision. The same difficulty was experienced in acetyl chloride and benzoyl chloride (*loc. cit.*). The results of these titrations are recorded in Table II, while the colour of the crystal violet in different solvents in the presence of the Lewis acids and bases is shown in Table I. The figures in column 6 of Table II have been arrived at by assuming the reagents to be 100% pure.

TABLE I

Indicator : Crystal violet.

| Solvent. | Colour in solvent. | $TiCl_4$. | $SnCl_4$. | Quinoline. | α-Picoline. | D.M.A. | Pyridine. |
|---|---|---|---|---|---|---|---|
| $POCl_3$ | Yellowish green | Deep yellow | Deep yellow | Violet | Violet | Purple | ... |
| $SOCl_2$ | Greenish yellow | Orange-yellow | Orange-yellow | Bluish green | ... | ... | Bluish green |
| $AsCl_3$ | Dirty green | Light orange | Light orange | Violet | Violet | Blue | ... |

TABLE II

Indicator : Crystal violet.

| Titrant. | Substance. | Conc. of the titrant (g. mol./litre). | Wt. of the substance. | Vol. of the titrant. Found. | Calc. | Colour of the indicator at the end-point. |
|---|---|---|---|---|---|---|
| | | | A. Solvent : $POCl_3$. | | | |
| $SnCl_4$ | Quinoline | 0 01871 | 0.820 g. | 3.85 c.c. | 3.87 c.c. | Light green |
| | Pyridine | 0.08916 | 0.068 | 4.70 | 4.82 | Greenish yellow |
| $TiCl_4$ | Quinoline | 0.16380 | 0.103 | 2.35 | 2.44 | Green |
| | Pyridine | 0.1638 | 0.072 | 2.80 | 2.78 | Bluish green |
| Quinoline | $SnCl_4$ | 0 13520 | 0 073 | 4.10 | 4.15 | Greenish yellow |
| | $TiCl_4$ | 0.19840 | 0.080 | 4.20 | 4.46 | Do |
| Pyridine | $SnCl_4$ | 0.25604 | 0.050 | 1.60 | 1.68 | Deep green |
| | $TiCl_4$ | 0.25604 | 0.071 | 3.30 | 3.27 | Greenish yellow |
| | | | B. Solvent: $SOCl_2$. | | | |
| $SnCl_4$ | Quinoline | 0.08626 | 0.066 | 2.70 | 2.95 | Orange-yellow |
| | Pyridine | 0.08626 | 0.029 | 1.85 | 2.12 | Do |
| $TiCl_4$ | Quinoline | 0.15099 | 0.032 | 0.80 | 0.82 | Do |
| | Pyridine | 0.15099 | 0.057 | 2.15 | 2.38 | Yellow |
| Quinoline | $SnCl_4$ | 0.14440 | 0.063 | 1.90 | 1.81 | Green |
| | $TiCl_4$ | 0.14440 | 0.033 | 1.45 | 1.37 | Light yellow |
| Pyridine | $SnCl_4$ | 0.25389 | 0.062 | 3.45 | 3.30 | Greenish yellow |
| | $TiCl_4$ | 0.25389 | 0.038 | 2.90 | 2.77 | Dirty green |
| | | | C. Solvent: $AsCl_3$. | | | |
| Quinoline | $SnCl_4$ | 0.18410 | 0.054 | 2.25 | 2.30 | Dirty green |
| | $TiCl_4$ | 0.22654 | 0.056 | 2.56 | 2.60 | Do |
| yridine | $SnCl_4$ | 0.34366 | 0.042 | 0.90 | 0.94 | Do |
| | $TiCl_4$ | 0.34366 | 0.040 | 1.30 | 1.22 | Do |
| α-Picoline | $SnCl_4$ | 0.33246 | 0.038 | 0.90 | 0.87 | Do |
| | $TiCl_4$ | 0.33246 | 0.056 | 1.80 | 1.77 | Do |
| Dimethyl-aniline | $SnCl_4$ | 0.26156 | 0.033 | 1.10 | 0.97 | Greenish yellow |
| | $TiCl_4$ | 0.26156 | 0.042 | 2.10 | 1.69 | Do |

## Discussion

Gutmann (*loc. cit.*) has postulated the auto-ionisation of phosphorus oxychloride as:

$$2POCl_3 \rightleftharpoons POCl_2^+ + POCl_4^-.$$

It has further been contended that the Lewis acids, when added to the solvent, combine with the anion to form complex ions and behave as acids, e.g.,

$$2POCl_3 + SnCl_4 \rightleftharpoons 2POCl_2^+ + SnCl_6^{2-}.$$

Organic tertiary bases, such as pyridine, quinoline etc., also behave as solvo-bases in $POCl_3$, and the reactions may be expressed as:

$$C_5H_5N + POCl_3 \rightleftharpoons C_5H_5N^+.POCl_2 + Cl^-.$$

The behaviour of the Lewis acids and bases has been found to be similar in thionyl chloride and arsenic trichloride (*loc. cit.*). Carbon tetrachloride and chlorobenzene are not expected to ionise; hence the Lewis acids and bases cannot act as solvo-acids and solvo-bases in such solvents.

Crystal violet, on addition to these solvents, furnishes coloured solutions and the colour of crystal violet varies considerably in the presence of the Lewis acids and bases. The results of these findings are recorded in Table I. In water (Rice *et al.*, *Anal. Chem.*, 1952, **24**, 1022), acetic acid (Fritz, *ibid.*, 1950, **22**, 1028; Seaman *et al.*, *ibid.*, 1951, **23**, 592), acetyl chloride (*loc. cit.*) and benzoyl chloride (*loc. cit.*), crystal violet exhibits bluish green colour at the neutralisation point of the strong acid and the strong base. But it is quite evident from Table I that in these solvents the colour of crystal violet is green, indicating the acidic character of the solvents. The variation in the colour of crystal violet in different solvents with the same acid or the same base shows that the acidity or basicity of the Lewis acids and bases is considerably affected by the nature of the solvent or in other words, it depends upon the solvo-acid or solvo-base, which is formed as a result of the initial reaction between the Lewis acid or base and the solvent.

In Table IIA are recorded the results of acid-base titrations in $POCl_3$. The bluish green colour of the indicator in the solvent was therefore taken as the colour at the end-point. The results of acid-base titrations in this solvent are encouraging and the speed of colour change indicates the reactions to be ionic in nature. It is remarkable to note that the indicator acts reversibly in this solvent.

The results of acid-base titrations in thionyl chloride are recorded in Table IIB. Luder *et al.* (*loc. cit.*) used basic solutions only as titrants and the end-point was taken as violet colour. The results of these titrations were high as these required consumption of more base to bring about violet colour in crystal violet. In the present investigation, the standard colour of the indicator at end-point in all the titrations has been considered to be that which it exhibits in the pure solvent. An attempt has also been made to study the reversible behaviour of crystal violet in thionyl chloride

(not studied by Luder *et al.*) which is excellently manifested in acetyl chloride (*loc. cit.*). In the case of acid titrants, the colour change of the indicator, close to the expected end-point, is always in some shade of yellow (Table IIB) and indicates slight excess of the acid used. But, when base solutions are used as titrants, the colour of the indicator, close to the expected end-point, appears to be a shade of green. In fact, the colour of the indicator in titrations in thionyl chloride due to its high acidic nature, and presumably on account of the difference in the strenghts of acids and bases, does not seem to follow the general pattern as it is not the same with the same acid-base pair, when the acid and base titrant solutions are used.

Arsenic trichloride acts as a polar solvent (*loc. cit.*). Crystal violet shows a dirty green colour in arsenic trichloride which leads to the conclusion that the solvent is, of course, less acidic as compared to phosphorus oxychloride and thionyl chloride. There is, however, one difficulty that, unlike the afore-mentioned solvents, it does not allow the use of crystal violet as a reversible indicator. But, when the solutions of bases-quinoline, pyridine, α-picoline and dimethylaniline are used as titrants, the results are in excellent agreement with the calculated values (Table IIc)

In carbon tetrachloride and chlorobenzene, it has been observed that these reagents behave as acids and bases with the indicator qualitatively but not quantitatively. Moreover, crystal violet is insoluble in $CCl_4$ and its solution in chlorobenzene has been used in the study of acid-base reactions in $CCl_4$. The obvious conclusion, which emerges so conspicuously from these titrations, is the ability of the solvent to provide ions which are essential for the typical acid-base neutralisation reactions in a solvent. The mode of reaction of quinoline and stannic chloride in $POCl_3$, $SOCl_2$ and $AsCl_3$ may be visualised as follows :

Phosphorus oxychloride :

$$2POCl_3 + SnCl_4 \rightleftharpoons SnCl_4.2POCl_3 \rightleftharpoons 2POCl_2^+ + SnCl_6^{2-}$$

$$POCl_3 + C_9H_7N \rightleftharpoons C_9H_7N.POCl_3 \rightleftharpoons C_9H_7N^+.POCl_2 + Cl^-$$

$$2C_9H_7N^+.POCl_2 + 2Cl^- + 2POCl_2^+ + SnCl_6^{2-} \longrightarrow 2POCl_3 + [C_9H_7N.POCl_3]_2.SnCl_6$$

Thionyl chloride :

$$2SOCl_2 + SnCl_4 \rightleftharpoons \quad 2SOCl_2 \quad \rightleftharpoons SnCl_4.2SOCl^+ + SnCl_6^{2-}$$

$$SOCl_2 + C_9H_7N \rightleftharpoons C_9H_7N.SOCl_2 \rightleftharpoons C_9H_7N^+.SOCl + Cl^-$$

$$2C_9H_7N.^+SOCl + 2Cl^- + 2SOCl^+ + SnCl_6^{2-} \longrightarrow 2SOCl_2 + [C_9H_7N.SOCl]_2.SnCl_6$$

Arsenic trichloride :

$$2AsCl_3 + SnCl_4 \rightleftharpoons SnCl_4.2AsCl_3 \rightleftharpoons 2AsCl_2^+ + SnCl_6^{2-}$$

$$AsCl_3 + C_9H_7N \rightleftharpoons C_9H_7N.AsCl_3 \rightleftharpoons C_9H_7N^+.AsCl_2 + Cl^-$$

$$2C_9H_7N^+.AsCl_2 + 2Cl^- + 2AsCl_2^+ + SnCl_6^{2-} \longrightarrow 2AsCl_3 + [C_9H_7N.AsCl_2]_2.SnCl_6$$

This may help in explaining the failure of titrations in carbon tetrachloride and chlorobenzene.

The results of these titrations in these solvents, when compared to those obtained in acetyl chloride and benzoyl chloride, indicate that, although all these solvents are of similar nature, the latter are superior as solvents for such titrations because the indicator is reversible and shows a gradation of colour just like that in water. However, the importance of these solvents as media for acid-base reactions cannot be underestimated.

CHEMISTRY DEPARTMENT,
PANJAB UNIVERSITY,
HOSHIARPUR.

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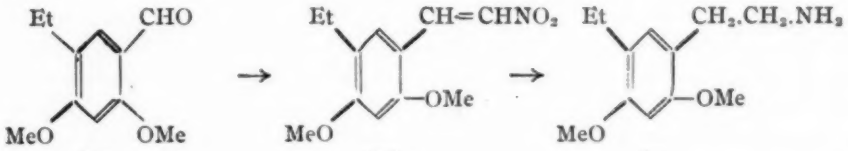
# SYNTHESIS OF POSSIBLE AMOEBACIDES. PART VI

By P. L. Kachru and C. N. Kachru

Synthesis of β- and α-(2:4-dimethoxy-5-ethylphenyl)-ethylamines and γ-(2:4-dimethoxy-5-ethylphenyl)-*n*-propylamine is described.

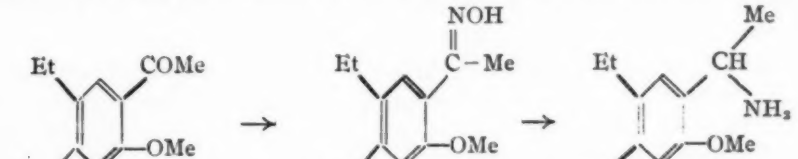
β-(2-Alkyl-4:5-dimethoxyphenyl)-ethylamine and its α-isomer were prepared by Kachru and Pathak (this *Journal*, 1957, **34**, 611, 768) out of which the hexyl derivatives were found to be as active as emetine when tested *in vitro* against *E. histolytica* (Kaushiva, *J. Sci. Ind. Res.*, 1957, **16C**, 224). The object of the present investigation is to find out whether *o*-dimethoxy nucleus is essential for amoebacidal activity. It is therefore considered worthwhile to prepare analogous amines with *m*-dimethoxy nucleus and to examine their amoebacidal activity. In addition, the substituted phenylpropylamine has also been prepared to determine the effect on the amoebacidal activity by increasing the aliphatic chain by one carbon atom. Synthesis of β-(I) and α-(2:4-dimethoxy-5-ethylphenyl)-ethylamines (II) and γ-(2:4-dimethoxy-5-ethylphenyl)-*n*-propylamine (III) is described in this paper.

β-(2:4-Dimethoxy-5-ethylphenyl)-ethylamine (I) has been prepared by subjecting 2:4-dimethoxyethylbenzene to Gattermann's aldehyde synthesis as modified by Adams, condensing the aldehyde (A) with nitromethane and subsequent reduction of the β-nitrostyrene (B) with lithium aluminium hydride.




(A) (B) (I)

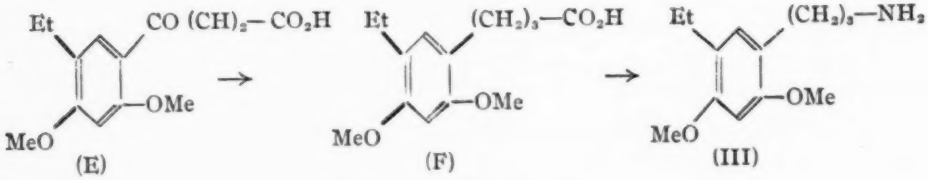
α-(2:4-Dimethoxy-5-ethylphenyl)-ethylamine (II) was obtained by reduction with sodium and alcohol of the ketoxime (D). The corresponding ketone (C) has been prepared by Friedel-Crafts' condensation of 2:4-dimethoxyethylbenzene with acetyl chloride in carbon disulphide solution in the presence of anhydrous aluminium chloride.




(C) (D) (II)

Synthesis of γ-(2:4-dimethoxy-5-ethylphenyl)-propylamine (III) has been achieved by condensing 2:4-dimethoxyethylbenzene with succinic anhydride, followed by the

Clemmensen reduction of the keto-acid (E) so formed, to substituted phenylbutyric acid (F), which through the amide and the subsequent Hofmann hypohalite reaction was converted into the desired amine.




*EXPERIMENTAL

*2 : 4-Dimethoxy-5-ethylbenzaldehyde* (A).—Dry HCl gas was passed for 1 hour into a mixture of 2 : 4-dimethoxyethylbenzene (55 g.), zinc cyanide (78 g.) and dry benzene (250 c.c.), placed in a three-necked flask fitted with a mercury-sealed stirrer and a reflux condenser, the flask being cooled in an ice-bath. Powdered anhydrous aluminium chloride (65 g.) was then added portionwise to the reaction mixture during 1 hour. The temperature of the bath was then raised to 50° which was maintained for 7 hours. Stirring and the passage of HCl were continued all the time. The mass was then left overnight, decomposed by ice, and the mixture refluxed on a water-bath for 2 hours. Benzene layer was separated out and the aqueous layer extracted twice with benzene. The combined benzene solution was washed with water, dried over calcium chloride and the residue after removal of benzene distilled in vacuum, b.p. 160°/5 mm, yield 33 g. (50%). The aldehyde solidified on cooling and it was crystallised from aqueous alcohol, m.p. 84°. (Found : C, 67.82 ; H, 7.45. $C_{11}H_{14}O_3$ requires C, 68.04 ; H, 7.21%). The *semicarbazone* was crystallised from dilute alcohol in white shining prisms, m.p. 201-202°. (Found : N, 16.5. $C_{12}H_{17}O_3N_3$ requires N, 16.3%).

*2 : 4-Dimethoxy-5-ethyl-β-nitrostyrene* (B).—Nitromethane (3.2 g.) and the above aldehyde (10 g.) were dissolved in methanol (20 c.c.) and cooled to 5°. To this mixture was added NaOH (5 g. in 10 c.c. water), previously cooled to 5°, at such a rate that the temperature remained below 10°. During the addition, the mixture was thoroughly stirred. After stirring for half an hour more, the mixture was poured dropwise into a large excess of HCl (dilute) with continuous stirring, when a yellow crystalline solid separated out. It was filtered, washed and crystallised from dilute alcohol, m.p. 63-64°, yield 5 g. (41%). (Found : N, 5.7. $C_{12}H_{15}O_4N$ requires N, 5.9%).

*β-(2 : 4-Dimethoxy-5-ethylphenyl)-ethylamine* (I).—To a slurry of $LiAlH_4$ (3.5 g.) in anhydrous ether (200 c.c.) was added 2 : 4-dimethoxy 5-ethyl-β-nitrostyrene (4.4 g.), dissolved in ether, at such a rate that the ether refluxed gently. The addition was completed in half an hour. The flask was then warmed on a water-bath and then left overnight. Excess of $LiAlH_4$ was decomposed by water and the ethereal layer dried over solid KOH. Dry HCl gas was passed through the ethereal solution when the

* Melting and boiling points are uncorrected.

*amine hydrochloride* separated as a solid. It was filtered, washed repeatedly with fresh ether and crystallised from ethyl acetate, m.p. 200°, yield 2 g. (42%). (Found : C, 58.4 ; H, 8.2 ; N, 5.9. $C_{12}H_{20}O_2NCl$ requires C, 58.7 ; H, 8.1 ; N, 5.7%). The *picrate* was crystallised from dilute alcohol in yellow needles, m.p. 195° (decomp.).

2 : 4-*Dimethoxy-5-ethylacetophenone* (C).—Finely powdered anhydrous aluminium chloride (100 g.) was gradually added to the well-cooled solution of acetyl chloride (30 g.) in $CS_2$ (200 c.c.) and after keeping for half an hour, 2 : 4-dimethoxyethylbenzene (40 g.) was slowly run in with constant stirring and cooling in ice. After keeping overnight, the mixture was heated on a steam-bath till HCl fumes ceased to evolve. $CS_2$ was distilled off and the residue decomposed by crushed ice. The product was extracted with benzene. The benzene solution was thoroughly and repeatedly shaken with dilute NaOH. The alkaline layer on acidification furnished the demethylated product (30 g.). The demethylated product was refluxed with dimethyl sulphate (60 g.) and excess of a solution of KOH for one hour, after which it was extracted with benzene. This benzene layer was mixed with the main benzene solution. The combined benzene extract was washed with water and dried over fused calcium chloride. Benzene was removed and the residual liquid distilled, b.p. 165°/4 mm. The ketone solidified in the receiver and was crystallised from aqueous alcohol, m.p. 67°, yield 35 g. (70%). (Found : C, 69.3 ; H, 7.9. $C_{12}H_{16}O_3$ requires C, 69.2 ; H, 7.7%). Its *semicarbazone* was crystallised from dilute alcohol, m.p. 161°. (Found : N, 15.6. $C_{13}H_{19}O_3N_3$ requires N, 15.8%).

2 : 4-*Dimethoxy-5-ethylacetophenone Oxime* (D).—Hydroxylamine hydrochloride (40 g.), crystallised sodium acetate (60 g.) and 2 : 4-dimethoxy-5-ethylacetophenone (20 g.) were dissolved in alcohol and refluxed for half an hour. The solution was chilled in ice when the oxime separated as white flakes. It was crystallised from dilute alcohol, m.p. 125°, yield 20 g. (93%). (Found : N, 6.5. $C_{12}H_{17}O_3N$ requires N, 6.3%).

α-(2 : 4-*Dimethoxy-5-ethylphenyl*)-*ethylamine* (II).—2 : 4-Dimethoxy-5-ethylacetophenone oxime (18 g.) was dissolved in absolute alcohol and reduced with metallic sodium (25 g.). The mass was cooled and acidified with HCl. Alcohol was removed by distillation under reduced pressure and the residual solid was dissolved in water. Any unchanged mass was removed by extraction with benzene. The aqueous layer was then basified with NaOH solution and the separated amine extracted with benzene. The benzene extract was dried over KOH, benzene removed and the residual liquid distilled in vacuum, b.p. 135°/3 mm, yield 7 g. (44%). (Found : N, 6.72. $C_{12}H_{19}O_2N$ requires N, 6.69%). The *amine picrate* was crystallised from dilute alcohol, m.p. 170°.

β-(2 : 4-*Dimethoxy-5-ethylbenzoyl*)-*propionic Acid* (E).—Succinic anhydride (20 g.) and powdered anhydrous aluminium chloride (54 g.) were dissolved in nitrobenzene (100 c.c.) with thorough shaking and cooling. The solution was placed in a flask provided with a reflux condenser and a calcium chloride guard-tube. 2 : 4-Dimethoxyethylbenzene (34 g.) was then slowly run in with thorough shaking. The reaction was allowed to proceed at room temperature. After 24 hours the complex was decomposed with ice and HCl. Nitrobenzene was removed by steam distillation,

The residue on cooling solidified. It was filtered, dissolved in dilute sodium carbonate solution and extracted with ether to remove non-acidic material. The alkaline layer was clarified by charcoal and, on acidification, the desired acid precipitated out. It was crystallised from dilute alcohol, m.p. 140°, yield 40 g. (74%). (Found : C, 63.4 ; H, 6.5. $C_{14}H_{18}O_5$ requires C, 63.1 ; H, 6.7%).

γ-(2 : 4-*Dimethoxy-5-ethylphenyl*)-n-*butyric acid* (F).—To amalgamated zinc (300 g.), prepared in the usual manner, were added water (100 c.c.), HCl (conc., 200 c.c.), toluene (100 c.c.) and β-(2 : 4-dimethoxy-5-ethylbenzoyl)-propionic acid (35 g.). The mixture was refluxed for 30 hours, HCl (conc., 25 c.c.) being added at the end of every six hours. Toluene layer was separated and the aqueous layer extracted twice with toluene. The combined toluene solution was shaken thoroughly with NaOH solution and the toluene steam-distilled off. The residual liquid was refluxed with dimethyl sulphate (10 c.c.) and activated charcoal, filtered and the filtrate acidified. A thick viscous oil separated which solidified on long chilling. The acid was dried at 40° and crystallised from methanol, m.p. 66°, yield 28 g. (87%). (Found : C, 66.35 ; H, 7.45. $C_{14}H_{20}O_4$ requires C, 66.66 ; H, 7.93%).

γ-(2 : 4-*Dimethoxy-5-ethylphenyl*)-n-*propylamine* (III).—Dry ammonia was passed through molten γ-(2 : 4-dimethoxy-5-ethylphenyl)-*n*-butyric acid (20 g.) at 200° for 2 hours. The hot mass was poured into water. The separated amide was washed and used as such for conversion into the amine. Sodium hypochlorite (400 c.c., 0.5*N*) was added to the amide. The mixture was continually stirred till the amide dissolved (3 hours) after which it was gradually warmed. Solid KOH (20 g.) was added and heating continued on a steam-bath. The amine separated as an oil which was extracted with benzene. The benzene extract after drying over solid KOH and removal of benzene was distilled in vacuum, b.p. 165°/5 mm, yield 5 g. (29%). The *amine hydrochloride* after crystallisation from ethyl acetate melted at 162°. (Found : C, 60.9 ; H, 8.8 ; N, 5.4. $C_{13}H_{22}O_2NCl$ requires C, 60.1 ; H, 8.6 ; N, 5.3%).

Thanks of the authors are due to Dr. Mata Prasad, Vice-Chancellor, Vikram University, for providing research facilities and to Dr. B. Pathak, Department of Applied Chemistry, Calcutta University, for his continued interest during these investigations.

School of Studies (Chemistry),
Vikram University,
Ujjain (M.P.).

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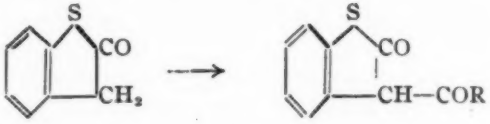
# SOME REACTIONS OF THIO-OXINDOLE

By J. N. Chatterjea and A. K. Mitra

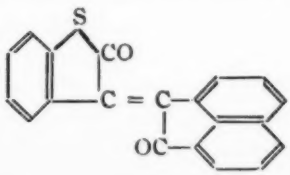
The acylation and condensation reactions of thio-oxindole have been studied.

The purpose of the investigation reported herein is to study the parallelism in properties between *iso*coumaranone and its sulphur analogue, thio-oxindole, towards acylation and condensation reactions. Glauert and Mann found that thio-oxindoles could be acylated at the 3- position by employing *NN'*-diphenylamidines (*J. Chem. Soc.*, 1952, 2127). In the present work, however, we find that *NN'*-diphenylbenzamidine cannot be used with success to benzoylate thio-oxindole. It is found that acylation in this series may be done with advantage by the use of acid anhydride—sodium salt combination. Thus, by employing sodium benzoate—benzoic anhydride, 3-benzoylthio-oxindole was prepared (cf. Chatterjea, this *Journal*, 1956, **33**, 175), and by using sodium acetate—acetic anhydride, 3-acetylthio-oxindole was similarly prepared.

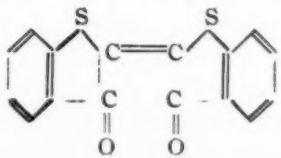



These acyl derivatives are largely enolic ; they afford copper chelates readily and impart a characteristic colour to alcoholic ferric chloride solution. These acyl derivatives, in contrast to acyl *iso*coumaranones, did not undergo the acid-catalysed rearrangement to thionaphthene derivatives (*ibid.*, 1957, **34**, 299) ; thio-oxindole-3-aldehyde, for example, on treatment with acids gave rise to thio-oxindole by hydrolysis.

Condensation of thio-oxindole with 1 : 2-dicarbonyl systems can be brought about with some difficulty. The thioindigoid (I) was obtained on condensation with acenaphthenequinone in acetic acid with catalytic amounts of hydrochloric acid for several weeks at the ordinary temperature. On condensation with thionaphthenequinone, a mixture was obtained from which thioindirubin (II) was isolated. It may be noted that the conden-

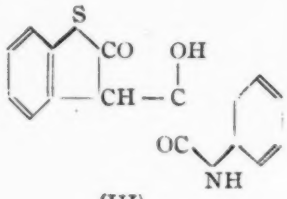



(I)

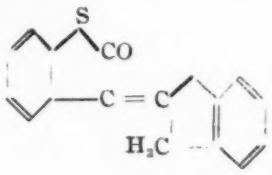



(II)

sation of thioindoxyl with thionaphthenequinone also leads to (II) (Friedländer, *Monatsh.*, 1908, **29**, 359) and Marschalk (*J. prakt. Chem.*, 1913, **88**, 227) obtained the same product by the condensation of *p*-dimethylamino-anil of thioindoxyl with thio-oxindole.



(III)



(IV)

The formation of (II) results by the condensation of α-carbonyl group of thionaphthenequinone, whereas in the reaction between *iso*coumaranone and coumaran-dione, the β-carbonyl group (position with respect to the hetero atom) takes part in the condensation (Chovin, *Compt. rend*, 1942, **215**, 466; *Bull. soc. chim.*, 1944, *v*, **11**, 82; Chatterjea, this *Journal*, 1959, **36**, 69). With isatin, thio oxindole furnished the addition product (III) (cf. Marschalk, *loc. cit.*).

Thio-oxindole underwent self-condensation on treatment with sodium hydride in benzene. The product, $C_{16}H_{10}OS_2$, is insoluble in cold alkali but dissolves on boiling; the compound, however, could not be regenerated from the alkaline solution. With acetic anhydride it yielded a mono-acetyl derivative and the compound remained unchanged on boiling with acids. On these grounds, the structure (IV) is advanced for the compound.

The structure is supported by the strong carbonyl absorption in I. R. at 5.82 μ (in carbon disulphide solution and in KBr pellet) and by the absence of hydroxyl group absorption. Thio-oxindole absorbs at 5.80 μ in nujol or in carbon disulphide solution. Clearly, the acetyl compound, mentioned above, is the enolic derivative (cf. self-condensation of coumaran 3-one: Fries and Pfaffendorf, *Ber.*, 1910, **43**, 212; 1911, **44**, 114).

## Experimental

*3-Acetylthio-oxindole.*—A mixture of thio-oxindole (0.4 g.), sodium acetate (0.2 g.) and acetic anhydride (3 c.c.) was heated on a water-bath for 1 hour and then water (15 c.c.) was added to the red product. The sticky mass separating was stirred for 1 hour with a saturated solution of sodium bicarbonate on the water-bath, filtered and acidified. Colorless crystals of the acetyl compound 0.15 g.) wer obtained as needles from aqueous alcohol, m.p. 105° (lit., m.p. 105°), showing a deep blue colour with ferric chloride. (Found: C, 62.1; H, 4.5. Calc. for $C_{10}H_8O_2S$: C, 62.5; H, 4.2%).

*3-Benzoylthio-oxindole.*—A mixture of thio-oxindole (1.0 g), benzoic anhydride (3.5 g.) and dry sodium benzoate (0.2 g.) was heated in an oil-bath at 120° for 2 hours. The entire mass was decomposed with water, left overnight and the gummy mass repeatedly extracted with alkali (5 × 10 c.c., 5%). The alkaline solution on acidification

*All m.p.s. are uncorrected.

afforded a mixture of benzoic acid and 3-benzoylthio-oxindole; the former was removed by taking advantage of its solubility in hot water. The compound was crystallised from alcohol in cream-coloured leaflets, m.p. 107°, developing a deep blue ferric chloride reaction. (Found: C, 71.3; H, 4.3. $C_{15}H_{10}O_2S$ requires C, 71.0; H, 3.9%).

*3-Thionaphthene-acenaphthylene-indigo* (I).—To a warm solution of thio-oxindole (0.5 g.) and acenaphthenequinone (0.5 g.) in acetic acid (8 c.c.) a drop of HCl (conc.) was added and the mixture left for several weeks. During this period the reddish colour of the solution gradually deepened but much of the unchanged acenaphthenequinone separated out. The dye (0.2 g.) was mechanically separated from the quinone and crystallised four times from acetic acid. The compound was obtained in darkish red shining needles, m.p. 241°, $\lambda^{max}_{xylene}$ 5140 Å. (Found: C, 76.6; H, 3.1. $C_{26}H_{10}O_2S$ requires C, 76.4; H, 3.2%).

*Condensation of Thio-oxindole with Thionaphthenequinone.*—A mixture of thio-oxindole (0.5 g.) and pure thionaphthenequinone (0.5 g.) in acetic acid (5 c.c.) was left for 6 weeks after the addition of a drop of HCl (conc.). The deep red product (m.p. 135-70°) that separated was collected and chromatographed in benzene solution on acid-washed alumina. Impurities were strongly held and thioindirubin was slowly eluted with benzene. The alumina layer containing the substance was separated, extracted with alcohol and the residue after the removal of the alcohol was crystallised from acetic acid. Thioindirubin was obtained as deep red needles (0.04 g.), m.p. 206° (lit. m.p. 205-207°). With sulphuric acid the compound developed a green colour.

*Condensation of Thio-oxindole with Isatin.*—To a solution of isatin (0.5 g.) and thio-oxindole (0.6 g.) in acetic acid (10 c.c.) was addded a drop of HCl (conc.) and the mixture left for 5 weeks. The colorless crystals of the product (III) (0.5 g.) separated from the brownish red solution. On crystallisation from acetic acid this was obtained as colorless prisms, m.p. 170° (Marschalk, *loc. cit.* records m.p. 155-60°), evolution of gas at 210°. (Found: C, 65.2; H, 3.9. Calc. for $C_{16}H_9O_2NS$: C, 64.7; H, 3.7%).

*Self-condensation of Thio-oxindole.*—To a suspension of sodium hydride (1.7 g.) in dry benzene (80 c.c.) was added a solution of thio-oxindole (5.5 g.) in benzene (50 c.c.). A brisk evolution of hydrogen took place in the cold. The mixture was refluxed on the water-bath for ½ hour, cooled, and excess of hydride decomposed with alcohol and then water was added. The alkaline solution on acidification afforded a gum which on treatment with alcohol solidified (1.5 g.). The filtrate on distillation in a current of steam furnished unchanged thio-oxindole (2 g.), leaving a brown resinous mass (1.5 g.). On crystallisation from acetic acid, the above self-condensation product (IV) was obtained as colorless needles (1.2 g.), m.p. 144°. [Found: C, 67.9; H, 3.9; M.W. (Rast, in camphor), 269. $C_{16}H_{10}OS_2$ requires C, 68.1; H, 3.5%; M.W., 282]. $\lambda^{max.}_{MeOH}$ 228 mμ (log ε 5.35), 316 mμ (log ε 5.12), 350 mμ (log ε 5.1)]. On attempted crystallisation from hot alcohol the entire mass turned red and a reddish insoluble material together with some gum separated out. The compound was insoluble in cold sodium hydroxide solution, but dissolved on boiling. With ferric chloride it gave a

yellow precipitate. On boiling with hydrochloric acid in acetic acid, the compound remained unchanged. The *acetyl* derivative was obtained by heating with acetic anhydride on the water-bath ; this was crystallised from acetic acid in colorless prisms, m.p. 100-101°. [Found : C, 66·9 ; H, 3·5. $C_{18}H_{12}O_2S_2$ requires C, 66.7 ; H, 3.7%). $\lambda_{MeOH}^{max.}$ 228 mμ (log ε 5.35), 305 mμ (log ε 5.08) and 360 mμ (log ε 4.88)]. On hydrolysis with mineral acids, the deacetylated product, m.p. 144°, was obtained.

CHEMICAL LABORATORY,
SCIENCE COLLEGE, PATNA.

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# SEARCH FOR NEW ANTISPASMODICS. PART VIII

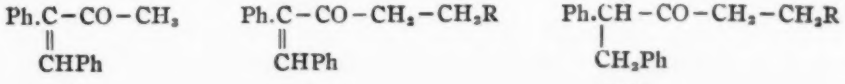
By T. N. Ghosh, Arun Bose and A. Raychaudhuri

Mannich bases (II and III) have been obtained. The base (III) has been reduced to the secondary alcohol (IV).

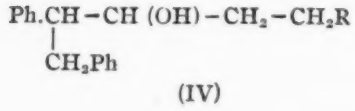
Denton *et al.* (*J. Amer. Chem. Soc.*, 1949, **71**, 2048) have synthesised a number of $\beta$-aminoketones of the general structure: $R_1-CO-CH(R_2)-CH_2-R_3$ (where $R_1$ is an aryl or heterocyclic group, $R_2$ is hydrogen or phenyl group and $R_3$ is a substituted amino group), some of which have equalled $\beta$-diethylaminoethyldiphenyl acetate hydrochloride (Trasentin) in antispasmodic action. Denton *et al.* (*ibid.*, 1949, **71**, 2050) converted these ketones into tertiary alcohols, possessing, in general greater antispasmodic activity than the parent ketones. Reference is made in this connection to the structure of adrenaline, which contains a secondary alcoholic group.

In view of the above observations it has been considered desirable to synthesise, as possible antispasmodics, several ketones and secondary alcohols containing tertiary amino group. In a previous communication (Raychaudhuri and Ghosh, this *Journal*, 1951, **28**, 566) the synthesis of such an amino-ketone, namely, $\alpha$-acetamido-$\beta$-diethylamino-(or piperidino)-propiophenone, which has been found to possess some antispasmodic action, has been recorded. However, reduction of this ketone with aluminium *iso*propoxide gave rise to the secondary alcohol which spontaneously underwent ring-closure to afford an oxazoline derivative (Ghosh and Dutta, *ibid.*, 1953, **30**, 865). The present communication describes the synthesis of several amino-ketones and the corresponding secondary alcohols as possible antispasmodics.

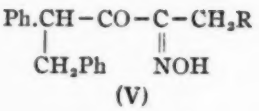
3-Phenyl-3-benzylidene-propan-2-one (I) (Goldschmidt and Krezmar, *Monatsh.*, 1897, **18**, 437; 1898, **19**, 406; 1901, **22**, 657), when subjected to the Mannich reaction with formaldehyde and piperidine hydrochloride, has furnished the hydrochloride of 4-phenyl-4-benzylidene-1-piperidinobutan-3-one (II). Hydrogenation of (II) over palladium-charcoal has yielded 4-phenyl-4-benzyl-1-piperidinobutan-3-one (III), accompanied by trace of a non-nitrogenous compound, not characterised. The base (III), on reduction with aluminium *iso*propoxide, has furnished the secondary alcohol, 4-phenyl-4-benzyl-1-piperidinobutan-3-ol (IV). With *n*-butyl nitrite the base (III) forms the *iso*nitroso derivative (V), which, on hydrogenation over Pd-C, furnishes the amino compound (VI). When treated with semicarbazide hydrochloride in presence of sodium acetate, (VI) forms the semicarbazone which spontaneously undergoes ring-closure with elimination of ammonia to give rise to the triazine derivative (VII).



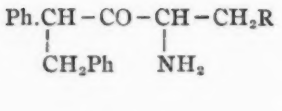
(I) (II) (III)



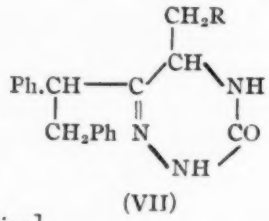
(IV)



(V)



(VI)



(VII)

[R = Piperidino]

The preliminary examination (A. N. Bose, *private communication*) on (II) and (III) shows that the compounds possess some antispasmodic activity, though rather toxic. Full details of the pharmacological examination will be reported elsewhere in due course.

## EXPERIMENTAL

*4-Phenyl-4-benzylidene-1-piperidinobutan-3-one* (II).—A mixture of (I, 11 g.), piperidine hydrochloride (10 g.), paraformaldehyde (2.4 g), HCl (conc., 0.3 c.c.) and anhydrous ethanol (90 c.c.) was heated under reflux on a steam-bath for 12 hours. The *hydrochloride* obtained was found to be sparingly soluble in water and was crystallised from ethanol in colorless microcrystalline powder (9 g.), m.p. 179-80°. The analytical sample was dried at 90-95° over $P_2O_5$ *in vacuo*. (Found : C, 74.12 ; H, 7.68 ; N, 4.08. $C_{22}H_{25}ON.HCl$ requires C, 74.26 ; H, 7.31 ; N, 3.94%). The base liberated from the above hydrochloride was crystallised from petroleum ether (b.p. 40-60°) in light yellow rectangular plates, m.p 48-49°. (Found : N, 4.12. $C_{22}H_{25}ON$ requires N, 4.39%).

The *picrate* was crystallised from ethanol in yellow needles, m.p. 169-70°. (Found : N, 10.43. $C_{22}H_{25}ON.C_6H_3O_7N_3$ requires N, 10.22%).

The *semicarbazone* was crystallised from ethanol in colorless rectangular plates, m.p. 233-34°. (Found : N, 14.72. $C_{23}H_{28}ON_4$ requires N, 14.89%).

*4-Phenyl-4-benzyl-1-piperidinobutan-3-one* (III).—Palladium-charcoal (10%, 0.1 g.) was added to a solution of the hydrochloride (6.9 g.) of (II) in anhydrous ethanol (200 c.c.) and the mixture was shaken at room temperature with hydrogen at atmospheric pressure, when one equivalent of hydrogen was gradually absorbed. The catalyst was removed by filtration and washed with ethanol. The filtrate and washings were combined and concentrated. The residue was dissolved in water and the aqueous solution washed with ether* and then basified with ammonium hydroxide. The product obtained was extracted with ether ; removal of the ether left a heavy liquid (5.9 g.). The base was purified by HCl-$NH_4OH$ treatment and the *oxalate* obtained was crystallised from anhydrous ethanol in colorless rectangular plates, m.p. 156-57°. [Found : N, 3.47. $C_{22}H_{27}ON.(CO_2H)_2$ requires N, 3.41%].

The *semicarbazone* separated on standing and was crystallised from ethanol in colorless, microcrystalline powder, m. p. 177-78°. (Found : N, 15.30. $C_{23}H_{30}ON_4$ requires N, 14.81%).

The *hydrochloride* was twice crystallised from ethanol-ether mixture in colorless needles, m.p. 146-47°. (Found : N, 4.27. $C_{22}H_{27}ON.HCl$ requires N, 3.91%).

The ether solution* was washed with water and dried (sodium sulphate). Removal of the ether left a non-basic liquid (0.4 g.), found to be devoid of nitrogen. It afforded a *semicarbazone* (m.p. 195-96°) and a 2 : 4-*dinitrophenylhydrazone* (m.p. 121-122°), but not any *p*-nitrobenzoate.

4-*Phenyl*-4-*benzyl*-1-*piperidinobutan*-3-*ol* (IV).—Aluminium *iso*propoxide was prepared by treating aluminium foil (3.5 g.) with a mixture of anhydrous *iso*propyl alcohol (40 c.c.), mercuric chloride (10.4 g.) and $CCl_4$ (1 c.c.).

To the above mixture, heated in an oil-bath at 100° under reflux, a solution of (III, 12.9 g.) in anhydrous *iso*propyl alcohol (110 c.c.) was added dropwise during 1 hour. After the addition was over, the mixture was refluxed for 2 hours, concentrated at 110-15° to half its volume to remove acetone (the presence of which was confirmed) and made up to its original volume with *iso*propyl alcohol. This process without alteration was repeated three times more. The solution was then concentrated to half its volume and the residual *iso*propyl alcohol was distilled off under reduced pressure. The residue was cooled and treated with an excess of 5% HCl (cold, dil.) when slight heat was generated After thorough trituration, the mixture was filtered and the filtrate basified, under cooling, with ammonium hydroxide. The gelatinous precipitate was filtered, thoroughly washed with water and extracted with boiling ethanol. The distillation of the ethanolic extract left a pasty mass, which was purified by HCl-$NH_4OH$ treatment. The product obtained was extracted with ether and removal of the ether left a thick brown liquid. The p-*nitrobenzoate* was crystallised from acetone in cream-coloured plates, m.p. 231-32°. (Found : N, 6.25. $C_{29}H_{32}O_4N_2$ requires N, 5.93%).

4-*Phenyl*-4-*benzyl*-2-*oximino*-1-*piperidinobutan*-3-*one* (V).—To a cooled solution of (III, 6 g.) in dry ether (25 c.c.) was added dropwise *n*-butyl nitrite (4.5 g.) under stirring. After keeping for some time, dry HCl gas was passed, when a solid separated which went into solution when further HCl was passed, affording a deep red solution. On keeping overnight in the cold, the ether was subsequently distilled off and the residue was poured into crushed ice. Sufficient water was added to dissolve the precipitated solid, and the solution, after being washed with ether, was basified with ammonium hydroxide solution. The solid obtained was crystallised from aqueous ethanol in cream-coloured needles, m.p. 135-36°. (Found : N, 8.38. $C_{22}H_{26}O_2N_2$ requires N, 8.0%).

4-*Phenyl*-4-*benzyl*-2-*amino*-1-*piperidinobutan*-3-*one* (VI).—A solution of (V, 3.5 g.) in anhydrous ethanol (200 c.c.) containing Pd-C (10%, 0.15 g.) was shaken in presence of hydrogen, when an equivalent quantity of hydrogen was gradually absorbed. The catalyst was removed by filtration and the filtrate was saturated with dry hydrochloric acid gas and distilled. The residue, on trituration with anhydrous ether, yielded a semi-solid mass which was dissolved in hot water, treated with charcoal and filtered. To the filtrate HCl (conc.) was added dropwise, when a cream-coloured microcrystalline solid was obtained, m.p. 182-83°. (Found : N, 7.76 ; Cl, 9.44. $C_{22}H_{28}ON_2.HCl$ requires N, 7.52 ; Cl, 9.53%). The same compound was obtained by conducting the above catalytic reduction in ethanol containing three equivalents of dry HCl gas.

*6-(Benzyl-phenylmethyl)-5-(piperidinomethyl)-3-hydroxy-4 : 5-dihydrotriazine* (VII).—A mixture of the hydrochloride (2 g.) of (VI), crystalline sodium acetate (5 g.), water (10 c.c.), semicarbazide hydrochloride (1.4 g.) and ethanol (95%, 30 c.c.) was warmed on a steam-bath for 20 minutes and left at room temperature. Gradually a solid separated which was crystallised from aqueous ethanol (charcoal) in colorless needles, m.p. 136-37°. (Found : C, 73.68 ; H, 7.87 ; N, 14.45. $C_{23}H_{28}ON_4$ requires C, 73.40; H, 7.44 ; N, 14.89%).

The authors are grateful to Dr. U. P. Basu, Director of the Institute, for his continued interest.

BENGAL IMMUNITY RESEARCH INSTITUTE,
CALCUTTA-6.

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# STUDIES IN CHROMIUM TUNGSTATE SOL. PART III. CHANGES IN EXTINCTION, *p*H AND ELECTRICAL CONDUCTIVITY OF COLLOIDAL CHROMIUM TUNGSTATE SOL DURING COAGULATION AT DIFFERENT STAGES OF DIALYSIS

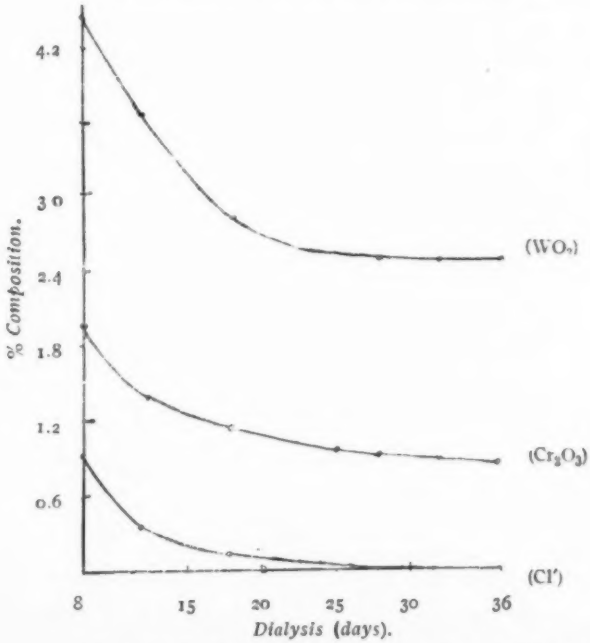
By P. C. Jain and S. N. Banerji

The mechanism of coagulation of chromium tungstate sol with an electrolyte, potassium sulphate, has been discussed with reference to the experimental results obtained from extinction, *p*H and electrical conductivity measurements.

Thomas and coworkers (*J. Phys. Chem.*, 1931, **35**, 27 ; *J. Amer. Chem. Soc.*, 1932, **54**, 847 ; 1934, **56**, 794) and Rai and Ghosh (*Proc. Nat. Acad. Sci. India*, 1954, **23**, 48, 142 ; 1956, **25**, 190, 195 ; *Kolloid Z.*, 1956, **142**, 104) studied the variation in *p*H and electrical conductivity of the sols of iron chromium and aluminium oxide during their coagulation with potassium sulphate.

Fig. 1

*% Composition of the sol with dialysis.*




In previcus communications (Jain and Banerji, *Proc. Nat. Acad. Sci., India*, 1958, **27**, 153 ; Saugar University Journal, 1958, **7A**, 35) we reported the results of changes in surface

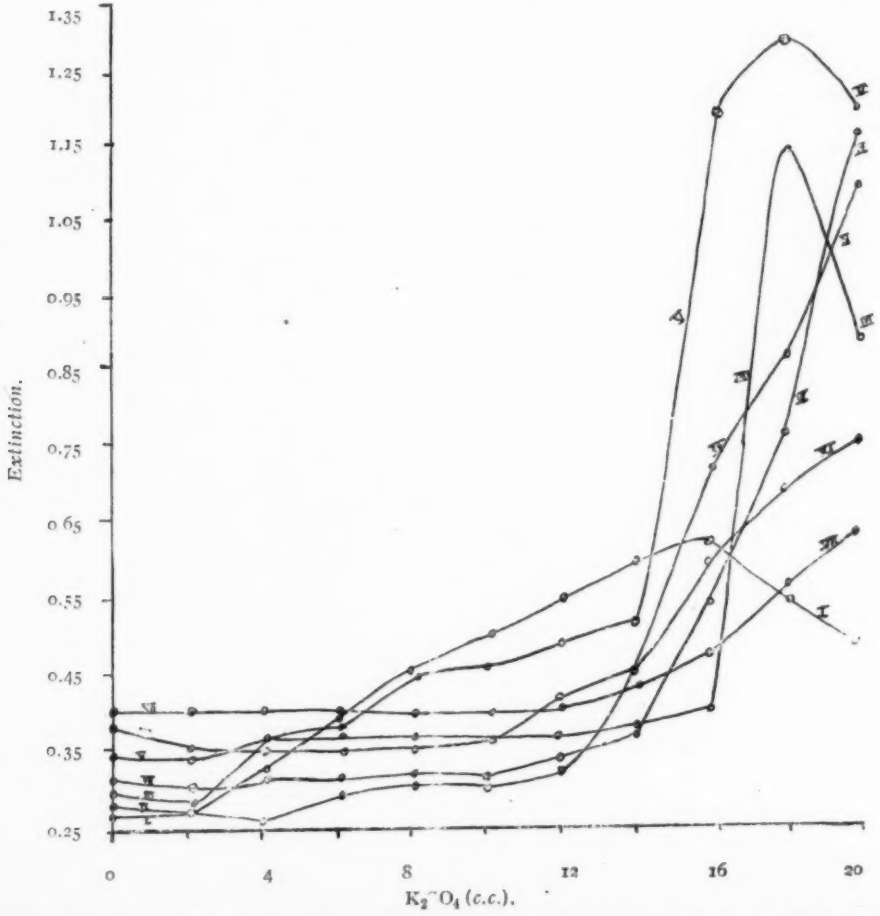
tension, viscosity, conductivity and stability of chromium tungstate sol under different stages of dialysis, dilution and temperature. We have studied here, with the help of extinction, *p*H and electrical conductivity measurements, the mechanism of coagulation of the sol under various stages of purity with an electrolyte such as potassium sulphate.

## EXPERIMENTAL

The preparation of the sol and the estimation of the constituents at different stages of dialysis were done in the same manner as reported earlier. Fig. 1 shows their variations with dialysis.

FIG. 2

*Variation of extinction by the addition of* $K_2SO_4$ *to the sol at diff. stages of purity.*




A series of eleven solutions of electrolyte in which the concentration of the precipitating component was systematically varied, the total volume being the same in each

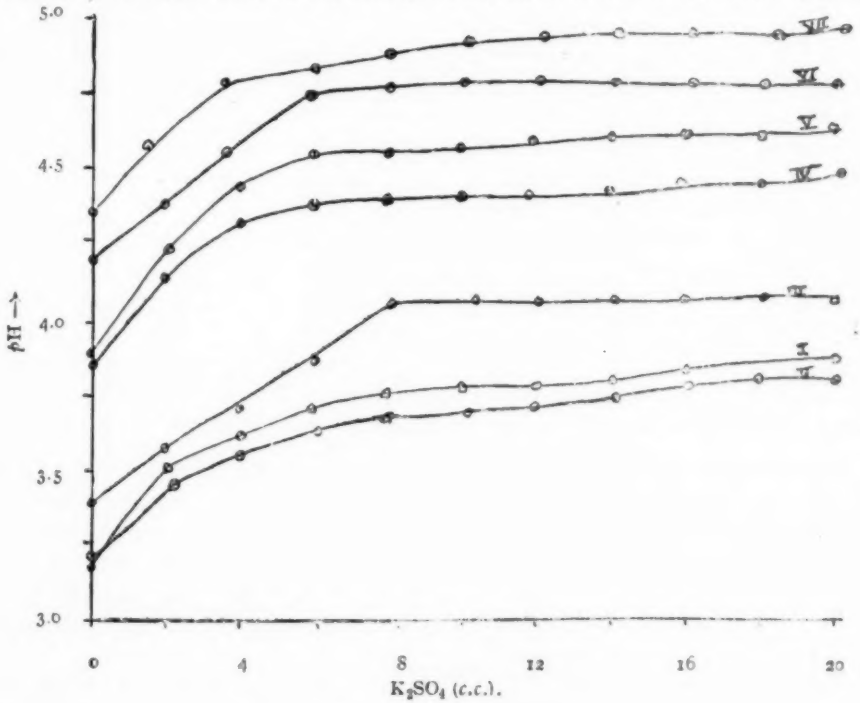
case (20 c.c.), was taken. Another series of the same number of beakers was arranged, each containing 20 c.c. of chromium tungstate sol. The mixing of the electrolyte solution and the sol in each beaker was carried out in exactly the same manner. Everytime, the readings were taken after five minutes of mixing.

Extinction measurements were carried out with a photoelectric colorimeter (Lichtelektrisches Kolorimeter, Modell V I) using red filter and 5 c.c. rectangular cuvette. The results are shown in Fig. 2, where the changes in extinction with electrolyte concentration at different stages of dialysis are plotted.

*p*H measurements were made with a Beckman *p*H-meter using glass and calomel (saturated) electrodes. The specific conductivities of the corresponding amounts of potassium sulphate present in the mixture of the sol were subtracted from the specific conductivities of the mixture of the sol and electrolyte. Fig. 4 represents the changes in the conductivity of the sol itself by the addition of the electrolyte.

FIG. 3

*Changes in the pH values by the addition of* $K_2SO_4$ *to the sol at diff. stages of purity.*




## DISCUSSION

Any attempt to study coagulation with optical methods needs firstly that the particles must be optically homogeneous and secondly, that the shape of the aggregated particles must be spherical if they are large, or ellipsoidal or plate-like if they are

small. Values of absorption coefficients of gold sol at various wave-lengths were calculated theoretically by Mie (*Ann. Physik*, 1908, **25**, 377) for spherical particles while Gans (*ibid.*, 1912, **37**, 881) made similar calculations for both ellipsoidal and plate-like particles, assuming particle size to be small. The theory of extinction method for flocculation has been well described by Treelstra (Thesis, Utrecht, 1941). Treelstra and Kruyt (*Koll.-Beih.*, 1943, **54**, 225), while studying the sols of $Fe_2O_3$ and AgI, found that with increasing concentration of electrolyte, a constant maximum flocculation wa reached. On further increasing the concentration, it begins to decrease due to t' e formation of loose flocks that scatter less light than massive sphere of the same weight.

The extinction-concentration curves (Fig. 2) show that in the beginning there seems to be no change in extinction by adding electrolyte. Coagulation is accelerated by increasing amounts of electrolyte until rapid coagulation starts. This is indicated by the sudden rise in the curves. However, at higher concentrations they begin to fall (although in some curves this stage is not reached) because of the formation of loose aggregates that scatter less light than those formed at smaller concentrations. In the latter cases the particles formed are relatively dense, since the repulsive action of the double layer is not completely removed. These particles behave as the Rayleigh scattering particles (*Phil. Mag.*, 1899, **47**, 375). In the absence of the repulsive action the flocks formed are irregular, rather loose and scatter little light, and thereby lower the extinction values.

A gradual increase of extinction with dialysis is mainly due to the aggregation of the sol particles, as suggested by us in our previous communications (*loc. cit.*) to explain increase in viscosity with dialysis.

Volkov and Rabinovitch (*Acta Physicochem.*, U.S.S.R., 1942, **17**, 14) found that with dialysis, the *p*H decreased from 7.24 to 6.08 in the case of gold sol, prepared by Zsigmondy's method. This is due to the removal of basic salts from the intermicellar liquid.

During dialysis of chromium tungstate sol there is a gradual removal from the intermicellar liquid of the stabilising electrolyte, chromium chloride, which is acidic in nature ; consequently the acidity of the sol decreases, *i.e.* *p*H increases.

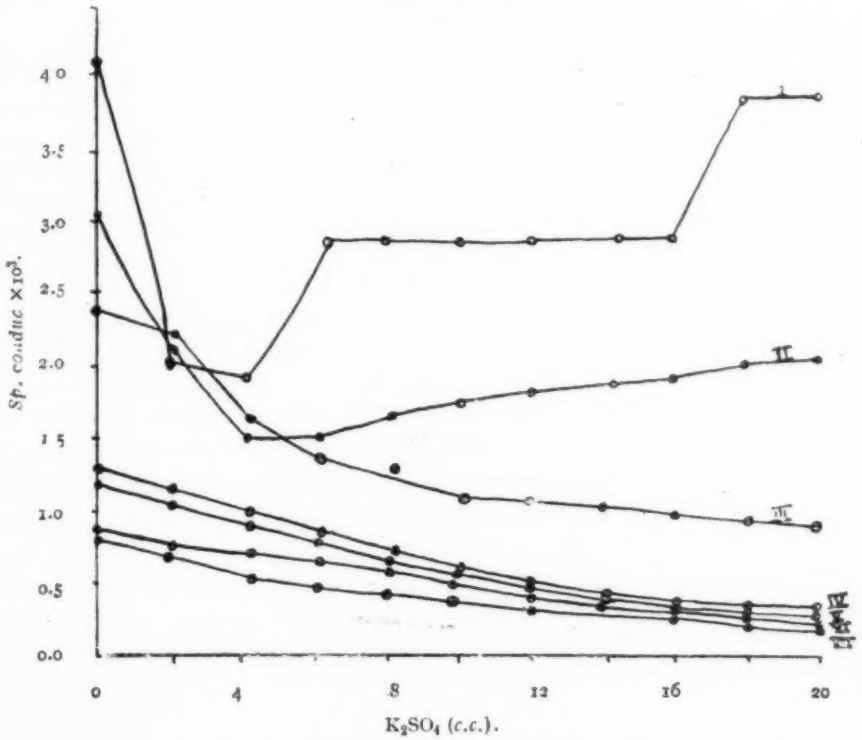
While studying the changes in *p*H values with the addition of potassium sulphate solution to iron, chromium and aluminium oxide sols, Thomas *et al.* (*loc. cit.*) found an increase. They suggested that the sol consisted of olated and oxolated oxychloride complex of the Werner type and that the increase in *p*H was due to the replacement of OH groups from the colloidal micelles by the anions of the added salts. Rai and Ghosh (*loc. cit.*), however, hold the view that this is due to the adsorption of the hydroxonium ions at the partially neutralised surface.

Taking in view the picture of the double layer, the potential determining ions (Lange and Berger, *Z. Elektrochem.*, 1930, **36**, 171), in this case $Cr^{3+}$ ions and possibly $H^+$ ions constitute the attached inner portion of the double layer with $Cl^-$ ions in the diffuse outer layer. On addition of sulphate ions that are more strongly adsorbed than chloride ions, the latter are displaced to a certain extent from the Stern layer (*ibid.*, 1924, **30**, 508). The sulphate ions take up a position closer to the inner layer when the

thickness of the shell is decreased (Tezak, *Chem. Abst.*, 1952, **46**, 9942). The result is that redistribution of the charges, from the uniform to non-uniform, within the shell takes place whereby the density of the charges and the probability of encounter between the coagulating and stabilising ions increase more than those in the peptised sol. At the same time, the partially neutralised colloid surface has a tendency to hold by adsorption such ions as are capable of producing the same electric charge as that of the colloid unit. The positively charged hydroxonium ions are therefore adsorbed on such surface of the colloid particle, thereby increasing $OH^-$ ion concentration in the system (Fig. 3).

FIG. 4.

*Variation of sp. conductance ($K_1$-$K_2$) by the addition of $K_2SO_4$ to the sol at diff. stages of purity.*




$K_1$ = Sp. conduc. of sol + electrolyte.

$K_2$ = ,, ,, of electrolyte.

The continuous decrease in specific conductivity of the sol, when pure, with the addition of the solution of potassium sulphate, may be explained as follows: Every sol particle is regarded as being surrounded by an ionic atmosphere (outer double layer), having a resultant charge, the sign of which is opposite to that of the sol particle itself.

When the particle moves, the oppositely charged ionic atmosphere exerts an electrostatic attraction, thus slowing down its motion. On addition of sulphate ions, the thickness of the double layer is decreased so that the electrostatic attraction between the inner and the outer layers of the shell will increase, causing further decrease in the mobilty of the particle. Also the ionic atmosphere with its associated water molecules moves opposite to the direction of the particle, producing an additional retardation to the motion of the particle. It is expected therefore that there will be a greater fall in conductivity until the stage of rapid coagulation is reached (Fig. 4). Smaller decrease observed thereafter is due to the aggregation of the sol particles when the radius of the resultant micelle will increase and its mobility will decrease.

CHEMICAL LABORATORY,
SAUGAR UNIVERSITY,
SAUGAR.

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# REACTIVE HALOGENONITROBENZENES AND THEIR DERIVATIVES. PART III. SOME DIHALOGENO-POLYNITROTOLUENES AND THEIR DERIVATIVES

By Shiam Sunder Joshi and Satya Prakash Gupta

Structures have been assigned to dinitration products of 2-chloro-1-bromo-5-methyl-, 1 : 2-dibromo-5-methyl-, 1-chloro-4-bromo-5-methyl- and 4-chloro-1-bromo-5-methyl-benzenes. Derivatives of a few halogenonitrobenzenes with ammonia, dimethylamine, diethylamine, aniline, *o*-, *m*- and *p*-toluidines, piperidine and potassium phenolate have been prepared and characterised.

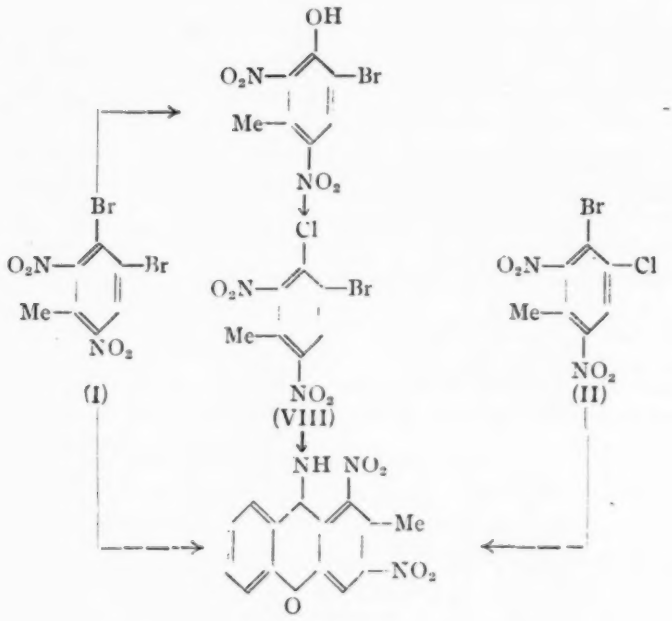
No structure has so far been assigned to some of the dihalogenodinitromethylbenzenes described in the literature. For this purpose, a few of them have now been obtained from halogenated toluidines by first replacing the amino group by a halogen atom and subsequently nitrating them. In this way 1 : 2-dibromo-4 : 6-dinitro-5-methyl*- (I) (Cohen and Dutt, *J. Chem. Soc.*, 1914, **105**, 502) and 2-chloro-1-bromo-4 : 6-dinitro-5-methyl*-benzenes (II) (Cohen and Smithells, *ibid.*, 1914, **105**, 1909) have been obtained from 2-bromo-4-methylaniline ; 1 : 4-dichloro-2 : 6-dinitro-5-methyl-(III) (Cohen and Dakin, *ibid.*, 1901, **79**, 1133) and 1-chloro-4-bromo-2 : 6-dinitro-5-methyl-benzenes* (IV) (Cohen and Smithells, *loc. cit.*) from 4-chloro-2-methylaniline ; 4-chloro-1-bromo-2 : 6-dinitro-5-methyl-* (V) (Cohen and Smithells, *loc. cit.*) and 1 : 4-dibromo-2 : 6-dinitro 5-methyl-benzenes (VI) (Cohen and Dutt, *loc. cit.*) from 4-bromo-2-methylaniline ; and 1 : 2-dichloro-4 : 6-dinitro-5-methyl-(VII) (Cohen and Dakin, *loc. cit.*) and 1-chloro 2-bromo-4 : 6-dinitro-5-methyl-benzenes (VIII) (Joshi and Gupta, this *Journal*, 1952, **29**, 199) from 2 chloro-4-methylaniline.

The reactivity of halogen atoms in the benzene nucleus, having at least two nitro groups in their *ortho*/*para* or the *ortho* positions, has been utilised for orientation of the products formed.

Thus, in the dinitro compound obtained from 2-chloro-1-bromo-5-methylbenzene, only the bromine atom is reactive (*vide infra*) and it is likely to be 2-chloro-1-bromo-4 : 6-dinitro-5-methylbenzene (II). This is confirmed by its forming a dinitromethylphenoxazine (IX), also obtained from 1-chloro-2-bromo-4 : 6-dinitro-5-methylbenzene (VIII) (Joshi and Gupta, *loc. cit.*).

On similar considerations, the dinitro product of 1 : 2-dibromo-5-methylbenzene can be presumed to be 1 : 2-dibromo-4 : 6-dinitro-5-methylbenzene (I). This formulation also agrees with the formation of 2-bromo-4 : 6-dinitro-5 methylphenol (Joshi and Gupta, *loc. cit.* ; cf. Borsche, *Ber.*, 1917, **50**, 1350), when a bromine atom is replaced by a hydroxyl group.

* Structure not established earlier.

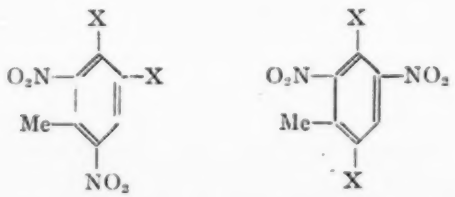



(IX)

The compound, obtained by the dinitration of 1-chloro-4- bromo-5-methylbenzene, is likely to be 1-chloro-4-bromo-2 : 6-dinitro-5-methylbenzene (IV) as only the chlorine atom in it is reactive and it furnishes with sodium acetate and acetamide, 4-bromo-2 : 6-dinitro-3-methylphenol (Joshi and Gupta, *loc. cit.*).

Similarly, the product of dinitration of 4-chloro-1-bromo-5-methylbenzene is 4-chloro-1-bromo-2 : 6-dinitro-5-methylbenzene (V).

In these compounds one of the two halogen atoms, as expected, readily reacts with ammonia, dimethylamine, diethylamine, aniline, *o*-, *m*- and *p*-toluidines, piperidine and potassium phenolate (Ullmann and Nadai, *Ber.*, 1908, **41**, 1876; Sane and Joshi, this *Journal*, 1932, **9**, 60 ; Siekel, *J. Amer. Chem. Soc.*, 1940, **62**, 750) furnishing the corresponding derivatives (Table II).




[X=Cl or Br]

TABLE I

| S.No. | Dihalogeno-5-methyl-benzenes used. | Dinitro-5-methylbenzenes obtained. | M.P. | Yield. | Analysis (%). Found. | Calc. |
|---|---|---|---|---|---|---|
| 1 | 1 : 2-Dichloro- | 1 : 2-Dichloro-4 : 6-dinitro- | 92° | 80% | Cl : 27 98 | 28 30 |
| 2. | 1-Chloro-2-bromo- | 1-Chloro-2-bromo-4 : 6-dinitro- | 84° | 85 | Cl+Br : 38.88 | 39 10 |
| 3. | 2-Chloro-1-bromo- | 2-Chloro-1-bromo-4 : 6 dinitro- | 127° | 85 | Cl+Br : 38.90 | 39.10 |
| 4. | 1 : 2-Dibromo- | 1 : 2-Dibromo-4 : 6-dinitro- | 129° | 80 | Br : 46.80 | 47.10 |
| 5. | 1 : 4-Dichloro- | 1 : 4-Dichloro-2 : 6-dinitro- | 101° | 85 | Cl : 28.04 | 28.30 |
| 6. | 1-Chloro-4-bromo- | 1-Chloro-4-bromo-2 : 6-dinitro- | 117° | 75 | Cl+Br : 38 79 | 39.10 |
| 7. | 4-Chloro-1-bromo- | 4-Chloro-1 bromo-2 : 6-dinitro- | 122° | 85 | N : 9.09 | 9.38 |
| 8. | 1 : 4-Dibromo- | 1 : 4-Dibromo-2 : 6-dinitro- | 124° | 80 | Br : 46.86 | 47.10 |

Three compounds have been separated from the nitration product of 1 : 3-dibromo-5-methylbenzene, viz., 1 : 3-dibromo-2 : 4-dinitro-5-methyl- (X) (Neville and Winther, *Ber.*, 1880, **13**, 967 ; Borsche and Trautner, *Annalen*, 1926, **447**, 16), 1 : 3-dibromo-4 : 6-dinitro-5-methyl- (XI) (*ibid.*) and 1 : 3-dibromo-2 : 4 : 6-trinitro-5-methyl-benzenes (XII) (Palmer, *Ber.*, 1888, **21**, 3501 ; Blankasma, *Rec. trav. chim.*, 1904, **23**, 127). Both the halogen atoms in them are reactive and are simultaneously replaced, affording disubstitution products (Table III). The disubstitution derivatives of 1 : 3-dichloro-2 : 4-dinitro-6-methylbenzene (XIII) (Seelig, *Annalen*, 1886, **237**, 163; Silberrad, *J. Chem. Soc.*, 1925, 2680), obtained by the nitration of 1 : 3-dichloro-6-methylbenzene, have also been described in Table III.

Identical derivatives were obtained from (II) and (VII), (I) and (VIII), (III) and (V), and from (IV) and (VI) (Table II). Identity of the derivatives from each pair has been established by mixed melting points and the analytical results.

## EXPERIMENTAL

*2-Chloro-1-bromo-5-methylbenzene.*—To aceto-*p*-toluide (50 g.), dissolved in acetic acid (100 c.c.), a solution of bromine (18 c.c.) in acetic acid (25 c.c.) was added with constant shaking. The mixture after keeping overnight and then on treatment with water furnished 3-bromoaceto-*p*-toluide (70 g.) ; it was crystallised from dilute alcohol, m.p. 117°.

The bromoacetotoluide (15 g.) on hydrolysis by boiling with four times its weight of HCl, diazotisation with a solution of sodium nitrite, followed by treatment with cuprous chloride and hydrochloric acid afforded 2-chloro-1-bromo-5-methylbenzene (9 g.). By adopting a similar procedure, 1 : 2-dibromo-5-methylbenzene was prepared from aceto-*p*-toluide and 1 : 4-dibromo-5-methyl- and 4-chloro-1-bromo-5-methylbenzenes from aceto-*o*-toluide.

TABLE II

*Derivatives of* 1 : 2-*dichloro- or* 2-*chloro*-1-*bromo*-4 : 6-*dinitro*-(I), 1 : 2-*dibromo or* 1-*chloro*-2-*bromo*-4 : 6-*dinitro*-(II), 1 : 4-*dichloro or* 4-*chloro*-1-*bromo*-2 : 6 *dinitro*-(III), *and* 1 : 4-*dibromo- or* 1-*chloro*-4-*bromo*-2 : 6-*dinitro*-5-*methylbenzenes* (IV).

| Sl. No. | Reactant. | Derivative. | (I) X=2-Chloro-4 : 6-dinitro- | | (II) X=2-Bromo-4 :6-dinitro- | | (III) X=4-Chloro-2 :6-dinitro- | | (IV) X=4-Bromo-2 : 6-dinitro- | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Colour. | M.P. | Colour. | M.P. | Colour. | M.P. | Colour. | M.P. |
| 1. | Ammonia | X-5-methylaniline | Dirty yellow needles | 114° | Yellow needles | *108° | Dirty yellow leaflets | 92° | Dirty yellow leaflets | 98° |
| 2. | Dimethylamine | X-5-methyl-dimethyl-aniline | Lemon-yellow needles | 80° | Lemon-yellow needles | 72° | Yellow prisms | 72° | Dirty yellow leaflets | 172° |
| 3. | Diethylamine | X-5-methyl-diethyl-aniline | Dirty yellow needles | 89° | Dirty yellow needles | 82.5° | Dirty yellow needles | 122° | Light brown needles | 126° |
| 4. | Aniline | X-5-methyl-di-phenylaniline | Pale yellow needles | 92° | Lustrous green leaflets | *132° | Orange lustrous needles | 98° | Orange-red needles | 116° |
| 5. | *o*-Toluidine | X-2′ : 5-dimethyl-di-phenylamir e | Canary-yellow needles | 128° | Orange needles | *145.5° | Saffron needles | 96° | Yellow needles | 108° |
| 6. | *m*-Toluidine | X-3′ : 5-dimethyl-di-phenylamine | Dull yellow needles | 120° | Lemon-yellow needles | 121° | Brick-red leaflets | 112° | Orange-red needles | 120° |
| 7. | *p*-Toluidine | X-4′ : 5-dimethyl-di-phenylamine | Orange-yellow needles | 101° | Orange-red needles | *134° | Orange lustrous leaflets | 136° | Orange leaflets | 124° |
| 8. | K-phenolate | X-5-methyl-diphenyl ether | White leaflets | 133° | Light yellow leaflets | 130° | Cream-yellow leaflets | 151° | White leaflets | 160° |
| 9. | Piperidine | X-5-methyl-phenyl-piperidine | Yellow prisms | 85° | Dirty yellow needles | *93° | Yellow needles | 85° | Yellow needles | 112° |

* Joshi & Gupta, this *Journal*, 1952, **29**, 99.

TABLE III

*Derivatives of* 1 : 3-*dibromo*-4 : 6-*dinitro*-5-*methyl*-(V), 1 : 3-*dibromo*-2 : 4-*dinitro*-5-*methyl*-(VI), 1 : 3 *dibromo*-2 : 4 : 6-*trinitro*-5-*methyl*-(VII), *and* 1 : 3-*dichloro*-2 : 6-*dinitro*-4-*methyl-benzenes* (VIII).

| Sl. No. | Reactant. | Derivatives. | (V) X=4 : 6-Dinitro-5-methyl- | | (VI) X=2 : 4-Dinitro-5-methyl- | | (VII) X=2 : 4 : 6-Triniro-5-methyl- | | (VIII) X=2 : 6 Dinitro-4-methyl- | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Colour. | M.P. | Colour. | M.P. | Colour. | M.P. | Colour. | M.P. |
| 1. | Ammonia | X-1 : 3-diamino-benzene | Yellow needles | 196° | Orange-yellow needles | 213·5° | Orange-yellow prisms | *225° | Golden needles | *256° |
| 2. | Dimethyl-amine | X-1 : 3-di-dimethyl aminobenzene | Pale yellow needles | 142° | Pale yellow needles | 138° | Lemon-yellow needles | 205° | Orange ,, | 160° |
| 3. | Diethylamine | X-1 : 3-di-diethyl-aminobenzene | Dirty yellow needles | 100° | Light brown needles | 152° | Dirty yellow needles | 168° | Yellow ,, | 136° |
| 4. | Aniline | X-1 : 3-dianilino-benzene | Orange-red needles | 176° | Garnet-red needles | 163° | Blood-red needles | 210° | Orange ,, | 128° |
| 5. | *o*-Toluidine | X-1 : 3-di-*o*-tolui-dinobenzene | Scarlet needles | 142° | Fawn needles | 166° | Saffron-yellow needles | 148° | Orange-yellow needles | 190° |
| 6. | *m*-Toluidine | X-1 : 3-di-*m*-tolui-dinobenzene | Blood-red prisms | 138° | Dark red needles | 148° | Scarlet-red needles | 152° | Do | 210° |
| 7. | *p*-Toluidine | X-1 : 3-di-*p* tolui-dinobenzene | Bright red needles | 180° | Brick-red needles | 192° | Garnet-red needles | 187° | Orange-red needles | 187° |
| 8. | K-phenolate | X-1 : 3-diphenoxy-benzene | Dirty white leaflets | 174° | Dirty white leaflets | 152° | White leaflets | 120° | White leaflets | 154° |
| 9. | Piperidine | X-1 : 3-dipiperidino-benzene | Yellow needles | 142° | Canary-yellow needles | 128° | Canary-yellow needles | 182° | Lemon-yellow leaftes | 92° |

* Blankasma, *Rec. trav. chim.*, 1904, **23**, 126; 1910, **29**, 415.

1 : 2-*Dichloro*-5-*methylbenzene*.—To a suspension of aceto-*p*-toluide (10 g.), obtained by adding to its solution in acetic acid (10 c.c.) and HCl (conc., 150 c.c.), potassium chlorate (4.5 g.), dissolved in the least amount of water, was added with constant shaking (20 mins.). After allowing it to stand for several hours, the white mass separating was crystallised from alcohol, furnishing 3 chloro-*p*-acetotoluide (10 g.), m.p. 114°. On hydrolysis and replacement of the amino group by chlorine, it afforded 1 : 2-dichloro-5-methylbenzene (6 g.), b.p. 205-206°. By adopting a similar procedure, aceto-*p*-toluide afforded 1-chloro-2-bromo-5-methyl-, and aceto-*o*-toluide, 1 : 4-dichloro-5-methyl- and 1-chloro-4-bromo-5-methylbenzenes.

*Dihalogenodinitro*-5-*methylbenzenes*.—Appropriate dihalogeno - 5 - methylbenzene (10 g.) and $H_2SO_4$ (*d* 1.84, 35 c.c.) were treated with fuming nitric acid (*d* 1.52, 15 c.c.) dropwise with vigorous shaking. It was first heated on a steam-bath and then on an oil-bath at 120° for several hours. The cooled product was poured on crushed ice. The pale mass separating was crystallised from alcohol or acetic acid, yielding shining crystals of dihalogenodinitro-5-methylbenzenes. All of them are pale white crystalline compounds. Their melting points, yield and analytical results are shown in Table I.

1 : 3-*Dibromo*-2 : 4-*dinitro*-, -4 : 6-*dinitro*-, *and* -2 : 4 : 6-*trinitro*-5-*methylbenzenes*.—To a suspension of 1 : 3-dibromo-5-methylbenzene (25 g.) in $H_2SO_4$ (*d* 1.84, 60 c.c.) fuming nitric acid (*d* 1.52, 15 c.c.) was added dropwise (15 mins.) with shaking and the product was heated on a water-bath for 4 hours. On cooling and pouring on crushed ice, the crude mass separating was repeatedly crystallised from acetic acid, furnishing 1 : 3-dibromo-4:6-dinitro 5-methylbenzene (6 g.) m.p. 157° (*loc. cit.*). The filtrate was concentrated nearly to dryness and the residue was dissolved in boiling alcohol. On cooling the solution, crystals of 1 : 3-dibromo-2 : 4-dinitro-5-methylbenzene were deposited (5 g.), m.p. 117° (*loc. cit.*). The alcoholic mother-liquor on heating to dryness and further nitration with an excess of fuming nitric acid and $H_2SO_4$ (conc.) yielded 1 : 3-dibromo-2 : 4 : 6-trinitro-5-methylbenzene (8 g.), m.p. 228° (*loc. cit.*).

2 : 4-*Dinitro*-3-*methylphenoxazine*.—A mixture of 2-chloro 1-bromo-4 : 6-dinitro-5-methylbenzene (1.5 g.), *o*-aminophenol (0.6 g.), anhydrous sodium acetate (2 g.) and absolute alcohol (30 c c.) was refluxed on a water-bath for 3 hours. It was then cooled and washed several times with water, HCl (dil.) and cold alcohol. The dark crude product on crystallisation from acetic acid yielded dark brown shining prisms of 2 : 4-dinitro-3-methylphenoxazine (1.1 g.), which decomposed at 280° without melting. (Found: N, 14.37. $C_{13}H_9O_5N_3$ requires N, 14.63%).

Similarly, 1-chloro-2-bromo-4 : 6-dinitro-5-methylbenzene with *o*-aminophenol in presence of anhydrous sodium acetate furnished a product which decomposed at 280° and was found identical, with 2 : 4-dinitro-3-methyl phenoxazine (mixed m.p.).

CHEMICAL LABORATORY,
MEERUT COLLEGE,
MEERUT, U.P.

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# ALIPHATIC AMINE COMPLEXES OF TRANSITION METALS. PART I. COMPOSITION AND STABILITY OF ZINC MONOMETHYLAMINE COMPLEXES IN SOLUTION

By C. S. Sharma and P. C. Sinha

The nature and stability of complexes formed by treating zinc sulphate with an excess of monomethylamine solution have been studied by the method of distribution of the base between two immiscible solvents. In solution zinc appears to be present largely as a complex ion containing three molecules of monomethylamine per atom of zinc. A detailed consideration of the results has led to some interesting conclusions.

One of the improtant methods of determining the nature and stability of complexes in aqueous solution is by the method of distribution of a base in two immiscible solvents. Dawson and McCrae (*J. Chem. Soc.*, 1900, **77**, 1239), Tamisier (*Bull. soc. chim.*, 1933, **53**, 127) and Sinha and Ray (this *Journal*, 1943, **25**, 247) used this method for the study of ammine complexes of copper, zinc and cadmium, and pyridine complexes of copper.

In the present investigation, chloroform and water have been used as the two immiscible solvents. The working temperature was chosen to be 35°, and partition coefficient of monomethylamine between the two solvents at this temperature was determined experimentally. Its value was found to be pratically constant, and independent of the initial concentration of the amine. Hence, it can be safely concluded that molecular complexity of monemethylamine in chloroform and water is the same.

## Experimental

The partition coefficient of monomethylamine at different concentrations was determined by shaking equal volumes of monomethylamine solution and chloroform to equilibrium in a thermostat maintained at 35° ± 0.02°, and analysing the two layers separately for the concentration of the amine, using methyl red as indicator.

Table I

*Partition of monomethylamine between chloroform and water at 35°.*
(All concentrations are in g. moles/litre).

| | | | | | |
|---|---|---|---|---|---|
| $C_1$ (aq. layer) ... | 0.7818 | 1.5612 | 1.952 | 2.346 | 3.126 |
| $C_2$ ($CHCl_3$ layer) .. | 0.1422 | 0.2828 | 0.3555 | 0.4260 | 0.5700 |
| $K_p = C_1/C_2$ (Partition coeff.) | 5.50 | 5.52 | 5.48 | 5.51 | 5.48 |

Mean value of $K_p = 5.5$.

After having determined the partition coefficient, a 0.5 *M* solution of zinc sulphate was prepared by dissolving appropriate amount of $ZnSO_4$, $7H_2O$ (Analar

quality) in a known volume of water. To 10 c.c. of this solution in each of the several glass-stoppered bottles varying volumes of 3.66 *N* monomethylamine solution were added, and the volume was made up to 50 c.c. with water in each case. Chloroform (50 c.c.) was added to each of the bottles and after equilibrium was reached in the thermostat, the concentrations of the amine in the two layers were determined as in the previous experiment. The concentration of the free amine in the aqueous layer was calculated by multiplying the concentration of the amine in the chloroform layer by the partition coefficient, and the concentration of fixed amine was calculated by taking the difference between the concentrations of the total and free amines present in aqueous layer in each case. From these data, average number of molecules of the amine, co-ordinated to each atom of zinc, was calculated.

TABLE II

*Distribution of monomethylamine between water and chloroform in presence of* 0.1 *M*-$ZnSO_4$ *at* 35°.

(All concentrations are expressed in g. moles/litre).

| $C_1$ (Conc. of Zn). | $C_2$ (Conc. of the amine in the $CHCl_3$ layer). | $C_3$ (Conc. of the amine in the aq. layer). | $C_4$ (Conc. of free amine $=Kp \times C_2$). | $C_5$ (Conc. of fixed amine. $=C_3-C_4$). | Ratio of Zn :amine. |
|---|---|---|---|---|---|
| 0.100 | 0.216 | 1.465 | 1.188 | 0.277 | 2.77 |
| 0.100 | 0.280 | 1.820 | 1.540 | 0.280 | 2.80 |
| 0.100 | 0.313 | 1.995 | 1.722 | 0.273 | 2.73 |
| 0.100 | 0.344 | 2.180 | 1.892 | 0.288 | 2.88 |
| 0.100 | 0.376 | 2.350 | 2.068 | 0.282 | 2.82 |
| 0.100 | 0.410 | 2.530 | 2.255 | 0.275 | 2.75 |
| 0.100 | 0.4415 | 2.710 | 2.429 | 0.281 | 2.81 |
| 0.100 | 0.4745 | 2.885 | 2.610 | 0.275 | 2.75 |
| 0.100 | 0.539 | 3.240 | 2.965 | 0.275 | 2.75 |
| 0.100 | 0.602 | 3.600 | 3.311 | 0.289 | 2.89 |

It was observed that at concentrations below the lowest, mentioned in the table, the complex partially broke down and zinc was precipitated, probably as the hydroxide. Above this concentration, however, the average number of molecules of monomethyamine attached to each zinc atom remained practically constant.

## DISCUSSION

As is well known, the nitrogen atom in methylamine is a better electron donor than that in ammonia due to electron-releasing effect of the methyl group.

In the experiments described above, the number of methylamine molecules combined with one atom of zinc was found to be independent of the concentration of monomethylamine. This fact can be explained on the basis of the following mechanism for the formation of the complex.

As methylamine solution is added to a solution of zinc sulphate, zinc hydroxide is first precipitated according to the equation :

$$ZnSO_4 + 2CH_3.NH_2 + 2H_2O = Zn(OH)_2 + (CH_3.NH_3)_2SO_4.$$

It is a well-known fact that zinc hydroxide molecule is linear with two $sp$ hybrid bonds. Now two more vacant $p$ orbitals are still available for formation of co-ordination compounds, and these can be progressively utilised by formation of $sp^3$ and $sp^3$ hybrid bonds respectively. As already pointed out, monomethylamine has stronger co-ordinating properties than ammonia ; hence, the molecules of the amine are progressively co-ordinated to zinc hydroxide, utilising the vacant orbitals, according to the following equations:

$$Zn(OH)_2 + CH_3.NH_2 \rightleftharpoons Zn(CH_3.NH_2)(OH)_2 \quad \ldots \quad (1)$$

$$Zn(CH_3.NH_2)(OH)_2 + CH_3.NH_2 \rightleftharpoons Zn(CH_3.NH_2)_2(OH)_2 \quad \ldots \quad (2)$$

With the progressive co-ordination of the molecules of the amine, the solubility of the hydroxide increases. As two molecules of the amine occupy the two vacant co-ordination positions of $Zn(OH)_2$, the perturbation caused by the two strongly electron-donating groups makes the covalent bonds between zinc and hydroxyl groups weaker, and the complex is dissociated to a small extent according to the equation :

$$Zn(CH_3.NH_2)_2(OH)_2 \rightleftharpoons [Zn(CH_3.NH_2)_2^{2+}] + 2OH^- \quad (2a)$$

so that $K_d$ for equation (2a) is given by :

$$K_d = \frac{[Zn(CH_3.NH_2)_2^{2+}]\,[OH^-]^2}{[Zn(CH_3.NH_2)_2\,(OH)_2]}.$$

The zinc *bis*-monomethylamine ion reacts with a third monomethylamine molecule, forming zinc *tris* monomethylamine ion according to equation (3) :

$$[Zn(CH_3.NH_2)_2]^{2+} + CH_3.NH_2 + H_2O \rightleftharpoons [Zn(CH_3.NH_2)_3\,(H_2O)]^{2+}$$

The equilibrium constant of this reaction is given by :

$$K_3 = \frac{[Zn(CH_3.NH_2)_3(H_2O)^{2+}]}{[Zn(CH_3.NH_2)_2^{2+}][CH_3.NH_2]}$$

$$= \frac{1}{K_d} \cdot \frac{[Zn(CH_3.NH_2)_3(H_2O)]^{2+}[OH^-]^2}{[Zn(CH_3.NH_2)_2(OH_2][CH_3.NH_2]}.$$

If the dissociation constant of monomethylamine is represented by $K_a$, then

$$K_a = \frac{[CH_3.NH_3^+][OH^-]}{[CH_3.NH_2]} \approx \frac{[OH^-]^2}{[CH_3.NH_2]}.$$

Using this result, we get

$$K_3 = \frac{K_a}{K_d} \times \frac{[Zn(CH_3.NH_2)_3(H_2O]^{2+}}{[Zn(CH_3.NH_2)_2(OH)_2]}.$$

The hydroxide of the zinc *tris*-monomethylamine ion remains completely dissociated, since the co-ordination affinity of Zn has been saturated by the three amine molecules (*vide infra*), and the hydroxyls are linked to the complex by purely ionic bonds. As already pointed out, $Zn(CH_3.NH_2)_2(OH)_2$ is only weakly dissociated.

Hence, the ratio of zinc atoms with three and two molecules of the amine respectively is very closely represented by

$$[Zn(CH_3.NH_2)_3(H_2O)]^{2+} : [Zn(CH_3.NH_2)_2(OH)_2]$$

and it has been shown above that this ratio is constant and independent of the concentration of the amine. As reactions (1) and (2), however, are clearly dependent on the concentration of the amine, on lowering the concentration of the amine, a critical concentration of the amine for each concentration of zinc ions is reached, after which further lowering of concentration of the amine results in the precipitation of the sparingly soluble zinc hydroxide, due to reversal of reactions (2) and (1).

The fact, that the average number of amine molecules attached to each zinc is about 2.8, suggests that the ratio of $[Zn(CH_3.NH_2)_3(H_2O)]^{2+} : [Zn(CH_3.NH_2)_2(OH_2)]$ is about 8 : 2 or 4 : 1.

Thus, the peculiar nature of the zinc monomethylamine complex in solution is explained. The fact that the complex ion is present only to an extent of 80% of the concentration of zinc atoms, suggests that the stability of the complex is comparatively low with repect to the zinc ammine complexes.

The fact that the zinc monomethlamine complex ion has no tendency to attach a fourth amine molecule, in contrast with zinc ammine complexes in solution, is in the opinion of the authors dependent on probably two factors: (*i*) the electron affinity of the zinc ion is more or less saturated by only three moleules of the amine due to electron-releasing effect of the methyl group, and (*ii*) the steric effect due to introduction of a methyl group in ammonia.

Department of Chemistry,
Patna University, Patna.

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# STUDIES ON THE METAL COMPLEXES OF HYDROXAMIC ACIDS. PART IV. COLOURED COMPLEXES OF IRON AND VANADIUM WITH QUINALDINOHYDROXAMIC ACID AND THEIR ANALYTICAL USES

By R. L. Dutta

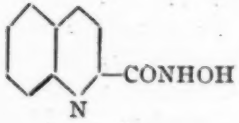
Quinaldinchydroxamic acid has been synthesised and its properties have been studied. A comparison of properties of the metal complexes of picolino-, nicotino-, *iso*nicotino- and quinaldinohydroxamic acids reveals a fair amount of gradation. The quinaldinohydroxamic acid complexes are characterised by comparative insolubility in water but ready solubility in organic solvents.

The reagent has proved to be sensitive for both iron and vanadium. Unlike with the other hydroxamic acids, it has been possible to determine iron and vanadium spectrophotometrically in the same sample with the help of this reagent. The Sandell sensitivity for the iron complex is 0.017 and that for the vanadium complex, 0.0137.

With a view to finding out more sensitive and efficient reagents for the colorimetric determination of metals, a systematic study on the metal complexes of pyridinohydroxamic acids was undertaken by the author. A detailed and systematic study has been made and the usefulness of the reagents for spectrophotometric determination of manganese, iron, vanadium and molybdenum has already been reported (Dutta, this *Journal*, 1957, **34**, 311 ; 1958, **35**, 243) in the case of nicotino- and *iso*-nicotino- hydroxamic acids.

In order to extend the studies to the quinolinohydroxamic acids and thereby to examine the weighting effect of the ligand, quinaldinohydroxamic acid hydrochloride has now been synthesised, and its behaviour towards various metallic ions examined.

The reagent, quinaldinohydroxamic acid, has been obtained by the interaction of the




ethyl ester of quinaldinic acid and hydroxylamine in absolute alcohol and the reagent finally obtained as the hydrochloride, the solubility of the latter in water being much lower than that of the hydrochloride of the other three pyridinohydroxamic acids. The aqueous solution of this hydroxamic acid hydrochloride has a light yellow colour, whereas those of the hydrochlorides of pyridinohydroxamic acids are colorless.

An account of the general reactions of quinaldinohydroxamic acid with various metallic ions is given in the Experimental. For the sake of comparison, the corresponding reactions of the three pyridinohydroxamic acids have also been presented. A fair amount of gradation in their properties is at once revealed. Thus, the solubility of the metal complexes, in general, falls off in the order: *iso*nicotino- → nicotino- → picolino- → quinaldino-hydroxamic acid, whereas the degree of extractability of the metal com-

plexes with organic solvents increases in the same order. The ease of formation of the red-violet manganese complex (which is believed to be a case of aerial oxidation, resulting in the formation of the $Mn^{III}$ complex) very distinctly falls off in this order. Thus, quinaldinohydroxamic acid produces with $Mn^{II}$ in ammoniacal medium a pale yellow precipitate which does not turn red-violet even on prolonged agitation. Picolinohydroxamic acid on prolonged shaking produces a faint red-violet colour, which soon turns turbid and precipitates manganic oxide. But nicotino- and *iso*nicotino-hydroxamic acids under similar conditions produce stable and sensitive red-violet colour, which has been utilised for the spectrophotometric estimation of the metal (Dutta, *loc. cit.*).

Ferric iron produces a violet colour at *p*H 1.2 and a red-coloured precipitate over the *p*H range 1.5 to 9.5. The precipitate dissolves above *p*H 10, producing a golden yellow colour. $Fe^{II}$ also produces the red precipitate, which dissolves in alkali to produce a golden yellow solution. For the determination of traces of iron, the optical density of the golden yellow colour ($\lambda_{max}$ 430 m$\mu$) may be measured over the *p*H range 11.0 to 12.5 against a reagent blank of similar *p*H. The red precipitate can be extracted with *iso*butyl alcohol over the *p*H range 3 0 to 9,0 and the optical density of the orange-red alcoholic extract measured at $\lambda_{max}$ 450 m$\mu$. The Sandell sensitivity of the colour reaction (for $Fe^{II}$ and $Fe^{III}$) is the same (0.01$\gamma$). Beer's law is closely followed by both the systems and the coloured products are perfectly stable.

In aqueous medium at *p*H 2.3 to 5.0, vanadium produces a dirty purple precipitate which dissolves at *p*H 5.9 to furnish a brown-coloured solution, the colour of which is discharged by the addition of alkali. The dirty purple precipitate is readily extractable in presence of excess reagent with higher alcohols, producing an intense orange-red solution, over the *p*H range 3.0 to 4.8. The coloured complex has an absorption maximum at 440- 450 m$\mu$. The system obeys Beer's law and shows a satisfactory stability (Sandell sensitivity 0.013 $\gamma$).

A study of the range of extractability of the iron and vanadium complexes has revealed that within the *p*H range 3.0 to 4.7, both iron and vanadium complexes are quantitatively extractable whereas within the *p*H range 7.0 to 9.0, iron alone is extracted. It has therefore been possible now to work out a method for the determination of iron and vanadium present in the same sample (vide Experimental). However, a more direct procedure would have been to extract out the iron complex at *p*H 7.0 to 9.0 and then to determine vanadium in the remaining aqueous layer by extraction at *p*H 3.0 to 4.7. But this procedure, although gave correct values for the iron present in the sample, yielded lower values for vanadium. This difference was traced to the retention of some vanadium in the alcoholic extract at *p*H 7.0 to 9.0.

## EXPERIMENTAL

Quinaldinic acid was prepared from quinaldine by following Hammick's method (*J. Chem. Soc.*, $192_3$, **123**, 2882).

*Ethyl Quinaldinate.*—Quinaldinic acid (20 g.) was taken in absolute ethyl alcohol (100 c.c., lime-dried and then distilled over sodium), $H_2SO_4$ (conc., 12-14 c.c.) added and the mixture heated under reflux on a water-bath for 5 to 6 hours. The

mixture was cooled, poured into ice, basified with ammonia and the separated ester extracted with ether. The ether extract was dried ($Na_2SO_4$) and the ether removed under reduced pressure ; yield 10 g.

*Quinaldinohydroxamic Acid Hydrochloride.*—A suspension of perfectly dry hydroxylamine hydrochloride (23.5 g. in 50 c.c. ethyl alcohol), taken in a three-necked flask fitted with an efficient mechanical stirrer, was treated with sodium ethoxide (8 g. sodium in 200 c.c. ethyl alcohol) under stirring. After an hour's stirring, the separated sodium chloride was removed by filtration. The filtrate was taken in a flask, treated with ethyl ester of quinaldinic acid (10 g.) and allowed to stand at 20° for 8-12 hours. Sodium ethoxide solution was kept in excess of the theoretical requirement in order to accelerate the reaction. Major portion of the hydroxamic acid separated as its sodium salt. The reaction mixture was then evaporated to dryness under reduced pressure on the water-bath. The residue was dissolved in hot water, acidified with HCl (dil.) and cooled. The crude quinaldinohydroxamic acid hydrochloride that separated was recrystallised from hot water containing a little HCl. It was finally dried in air. It forms pale yellow silky flakes, m.p. 205-206°. (Found : N, 12.3. $C_{10}H_8O_2N_2.HCl$ requires N, 12.5%). It is slightly soluble in cold water but more so in hot water and in alkali solutions.

The reactions of quinaldinohydroxamic acid together with those of picolino-, nicotino- and *iso*nicotino-hydroxamic acids are recorded in Table I.

The reagent was found to be colorimetrically sensitive towards iron and vanadium, but not to uranium, titanium and molybdenum. With manganese it produced no red-violet coloration, differing thereby from nicotino- or *iso*nicotino-hydroxamic acid.

A 1% solution of the reagent was prepared in hot water ; the solution was allowed to cool down to room temperature and then used for the spectrophotometric determinations.

### *Determination of Iron*

$Fe^{III}$ solution was prepared from ferric nitrate ; its iron content was determined gravimetrically as oxide. $Fe^{II}$ solution was prepared by weighing G. R. ferrous ammonium sulphate. These solutions were appropriately diluted.

A Unicam SP 600 spectrophotometer was used for the measurement of the optical density in 1 cm cells, unless otherwise mentioned.

*Optimum Wave-length for Measurement of the Optical Density.*—The optical density values at the different wave-lengths of the coloured products (Fe content 8γ per c.c.) in presence of a large excess of the reagent and at *p*H 11.5 are presented in Fig. 1 together with that of the same amount of the reagent at the same *p*H. It appears that the absorption maximum of the coloured product lies at 430-440 mμ, where the reagent also shows absorption. Measurements were therefore made against the reagent blank of similar *p*H. In the figure are also shown the O.D. values of the ferric (ferrous) quinaldinohydroxamate extracted from aqueous medium (*p*H 4.82) with *iso*butyl alcohol. The absorption maximum lies at 450 mμ.

*Effect of pH and Reagent Concentration on the Colour Intensity.*—The extraction of the red-coloured precipitate from aqueous medium with *iso*butyl alcohol was found to be

TABLE I

*Reactions of* isonicotino-, nicotino-, picolino- *and* quinaldino-hydroxamic acids *with metallic ions.*

[H stands for hydroxamic acid]

| Metal ions. | *iso*Nicotino-H (I). | Nicotino-H (II). | Picolino-H (III). | Quinaldino-H-(IV). |
|---|---|---|---|---|
| $Mn^{2+}$ | An intense red-violet colour in presence of NaOH or $NH_4OH$. Colour does not appear in presence of $NH_2OH$ or $N_2H_4$ nor in an atmosphere of $CO_2$. Possibly an $Mn^{III}$ derivative—colour, not extractable with organic solvents. | Same as in (I). | A faint red-violet colour in presence of NaOH or $NH_4OH$ only on prolonged shaking with air. This colour decomposes on standing to $Mn(OH)_3$. | A pale yellow ppt. appears in presence of $NH_4OH$ and does not change even on prolonged shaking; possibly an $Mn^{II}$ derivative. |
| $Fe^{3+}$ | Violet colour at *p*H 1-2, wine-red at *p*H 2.5-3 and golden yellow above *p*H 4.0. The coloured complex is only partially extractable with organic solvents at *p*H 3-6 but not in the alkaline range. | Same as in (II). | Violet colour at *p*H 1-2 ; a red ppt. over the *p*H range 2.5 to 9.5. The ppt. dissolves at *p*H 10 to form a golden yellow soln. The red ppt. is extractable with higher alcohols but partition coeff. is not very favourable. The ppt. is soluble in pyridine. | Same as in (III). The red ppt. appears at *p*H 1.5 and is very readily soluble in higher alcohols and in pyridine. |
| $Fe^{3+}$ | A golden yellow colour above *p*H 4 ; its behaviour is similar to that of the corresponding $Fe^{3+}$ complex. | Same as in (I). | A red ppt. persisting over the *p*H range 2.5 to 9.5. Its behaviour is similar to that of the corresponding $Fe^{3+}$ ppt. | Same as the red ppt. obtained from the $Fe^{3+}$ soln. |
| $V^{5+}$ | In dil. aq. medium a bluish purple colour at *p*H 2.5-3.5 and a bright purple colour at *p*H 7.6-8. In 50% ethanol, a dirty yellow colour in acid medium and a bright purple colour in alkaline medium. The bluish purple colour in aq. medium is only partially extracted with higher alcohols, but the bright purple colour is not extractable. | In dil. aq. medium a dull purple colour at *p*H 3 and a bright purple colour at *p*H 8.0. In 50% ethanol, a bright golden yellow colour at *p*H 3 and a bright purple colour at *p*H 8.0. The dull purple colour in aq. medium is extractable with higher alcohols affording bright golden yellow extract, but the colour in alkaline medium is not extractable. | Same as in (II). | In dil. aq. medium at *p*H 2.3-5.0 a dirty purple ppt. appears ; it dissolves to produce a brown soln. at *p*H 5.9. The dirty purple ppt. is readily extractable with higher alcohols affording a bright golden yellow extract. |

TABLE I (contd.)

| Metal ions. | *iso*Nicotino-H (I). | Nicotino-H (II). | Picolino-H (III). | Quinaldino-H (IV). |
|---|---|---|---|---|
| $Mo^{5+}$ | In not too dilute solutions at *p*H 3.0, a fine yellow ppt. appears; it dissolves above *p*H 5 producing a yellow soln. This is destroyed by alkali. | Same as in (I). | Same as in (I). | Even in dil. solns. a yellow ppt. appears at *p*H 2.6; it dissolves at *p*H 5 affording a clear yellow soln. The colour is not as sensitive as those of (I) (II, & (III). |
| $UO_2^{2+}$ | At *p*H 4.5, an orange-yellow ppt. appears in not too dilute solns. The ppt. dissolves at higher *p*H, producing a yellow soln. | Same as in (I). | Same as in (I). | Same as in (I). |
| $Ti^{4+}$ | At *p*H 5, a yellow ppt. is formed in conc. solns. This is decomposed by acids, but it dissolves at higher *p*H to afford a yellow soln. | Same as in (I). | Same as in (I). | Same as in (I). |
| $Zr^{4+}$ | No reaction. | No reaction. | No reaction. | A yellow ppt. appears in weakly acid medium. |
| $Cu^{2+}$ | At *p*H 5, a leaf-green ppt. is formed, which dissolves in alkali to afford a brownish soln. This again decomposes leaving copper oxide. | A leaf-green ppt. at *p*H 5 which dissolves in alkali, making a pale blue soln., which decomposes on standing to copper oxide. | A dark green soln. under similar condition, which changes to an unstable red colour in presence of alkali. | A yellow-brown gummy substance in weakly acid or alkaline soln. |
| $Co^{2+}$ | At *p*H 6, a light pink ppt. appears in conc. soln; it dissolves in alkali producing a brown soln. | Same as in (I). | Produes a red to yellow soln. at *p*H 7 or above. | Same as in (III). |
| $Hg^{2+}$ | No reaction. | No reaction. | At *p*H 7, a fine light yellow silky ppt. appears. | Same as in (III). |
| $Ce^{4+}$ | Pale red soln. in alkaline range. | Same as in (I). | Same as in (I). | Same as in (I). |

N.B. No perceptible reaction occurs with $Pb^{2+}$, $Ca^{2+}$, $Ni^{2+}$, $Nb^{5+}$ or $Ta^{5+}$.

quantitative over a very wide range of *p*H, 3.0 to 9.0. Above *p*H 10, the precipitate went into solution, producing a golden yellow colour, which maintained constant optical density over the *p*H range 11.0 to 12.5.

Variation of the reagent concentration at *p*H 11.0 showed that an amount at least twelve times the molar proportion of iron was necessary for maximum colour formation.

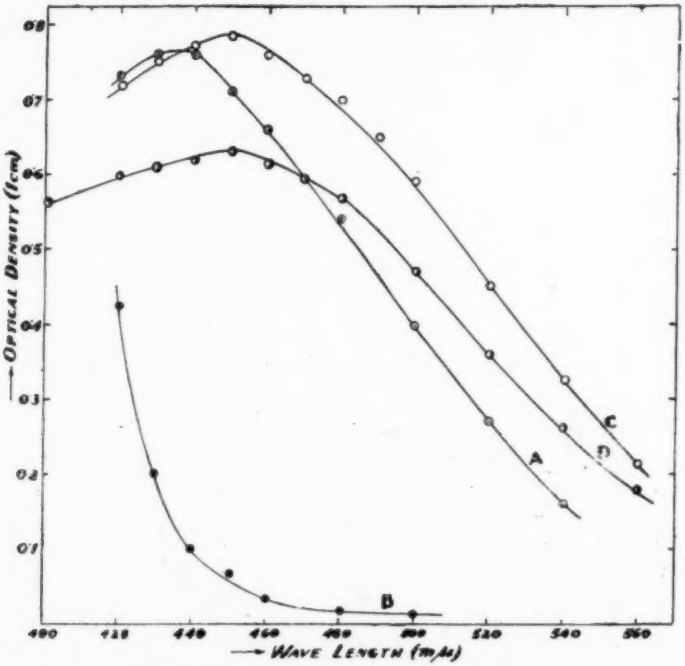
*Adherence to Beer's Law.*—The golden yellow colour, as also the orange-red alcoholic extract, obeyed Beer's law over a wide range, 1γ to 8γ Fe/c.c.

*Sandell sensitivity* : 0.01γ Fe/cm$^2$.

*Influence of Foreign Ions on the Colour System.*—The golden yellow colour formed in the alkaline range is more useful for the determination of iron than the extraction procedure, in the presence of foreign ions. In the presence of titanium (50γ) and uranium (60γ), the colour intensity should be measured at 500 mμ. Vanadium and molybdenum do not interfere even when present in considerable amounts. Copper, nickel and cobalt interfere.

FIG. 1.

*Absorption spectra.*




Curve A: Iron quinaldinohydroxamate (8γFe/c.c.) at *p*H 11.5.

Curve B: Quinaldinohydroxamate at *p*H 11.5; 1% solution.

Curve C: *iso*Butyl alcohol extract of aqueous iron quinaldinohydroxamate (*p*H of the aqueous medium 4.82); 8γFe/c.c.

Curve D: *iso*Butyl alcohol extract of aqueous vanadium quinaldinohydroxamate (*p*H of the aqueous medium 4.58); 8γV/c.c.

*Determination of Vanadium*

The optical density values of the golden yellow vanadium quinaldinohydroxamate, extracted out of aqueous medium (*p*H 4.58) with *iso*butyl alcohol, are shown in Fig. 1. The coloured complex showed its absorption maximum at 450 m$\mu$. The measurements of optical density were made against *iso*butyl alcohol. The optimum *p*H (of the aqueous medium) for extraction of the coloured product was 3.0 to 4.7. For maximum colour formation, a reagent concentration of about twenty times the molar proportion of vanadium was required. The coloured product obeyed Beer's law and was prefectly stable (Sandell sensitivity 0.013$\gamma$V/cm$^2$). Titanium, uranium and molybdenum should not be present beyond 25$\gamma$/c.c., and in their presence, the optical density of the alcoholic extract should be measured at 500 m$\mu$ in order to minimise the error due to the other absorbing species. Copper, nickel and cobalt interfere.

*Determination of Vanadium and Iron in presence of each other*

To an aliquot of the solution containing iron and vanadium (total amount not exceeding 0.2 mg.) was added an excess of quinaldinohydroxamic acid hydrochloride (5 c.c., 1% solution), diluted to about 50 c c., *p*H adjusted near about 4.0 and the complex extracted with three or four 5 c.c. portions of *iso*butyl alcohol. The extracts were collected in a 25 c.c. flask and the volume made up with the alcohol. The solution was then passed through a filter paper to retain the traces of water and its optical density measured in a 1 cm cell at 450 m$\mu$ against a similarly prepared reagent blank.

A similar aliquot was again taken, excess reagent added, *p*H adjusted within 7.0 to 9.0, the coloured product extracted with *iso*butyl alcohol and optical density measured at 450 m$\mu$ in a 1 cm cell. This determination in conjunction with a Beer's law curve provided the amount of iron present in the sample.

The optical density due to iron alone was then subtracted from the O.D. of the extract (at *p*H 4.0). The difference gave the O.D. of vanadium present in the sample, whence from the Beer's law curve of vanadium complex, the vanadium content of the sample was calculated. Satisfactory results were obtained and the error did not exceed 2%.

The studies on the analytical properties of hydroxamic acids have been extended to anthranilohydroxamic acid (*o*-aminobenzohydroxamic acid) in an effort to examine the modifications in properties which might result from the substitution of the acidic OH group of the salicylohydroxamic acid by a basic $NH_2$ group. The reactions of this reagent will be reported in due course.

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INORGANIC CHEMISTRY LABORATORY,
INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE,
CALCUTTA-32.

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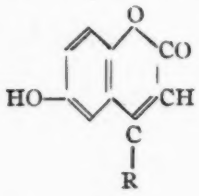
# SULPHINATION. PART III. SULPHINATION OF 6-HYDROXY-COUMARIN AND 4-METHYL-6-HYDROXYCOUMARIN

By R. N. Usgaonkar and G. V. Jadhav*

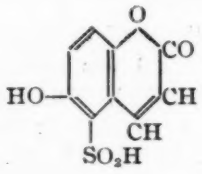
The action of thionyl chloride on 6-hydroxycoumarin in presence of anhydrous aluminium chloride leads to the formation of sulphinic acid, while no reaction takes place on 4-methyl-6-hydroxycoumarin.

6-Hydroxycoumarin (I, A) condensed with thionyl chloride in presence of anhydrous aluminium chloride to afford a poor yield of sulphinic acid (II). Attempts to sulphinate 4-methyl-6-hydroxycoumarin (I, B) under the same conditions met with failures, unchanged coumarin (I, B) having been recovered from the mixture.



(I)

[A : R=H; B : R=Me]



(II)

The sulphinic acid obtained from (I, A) is assigned the constitution of 6-hydroxy-coumarin-5-sulphinic acid (II) from the following considerations. The sulphinic acid and its derivative exhibit coloration with alcoholic ferric chloride showing $-SO_2H$ group to be either in position '5' or '7' (positions *ortho* to hydroxyl group) of the coumarin (I,A). The chance of $-SO_2H$ group to enter the position '7' is considered rather remote, otherwise 4-methyl-6-hydroxycoumarin (I, B) would have also reacted to furnish the sulphinic acid since position '7' is alike in both (I,A) and (I,B). The position '5' in coumarin (I,B) is under the influence of steric effect of methyl group in position '4' which renders it less accessible to a new substituent, while no such effect is there on position '5' of coumarin (I,A). During sulphonation of these coumarins (I,A) and (I,B) with chlorosulphonic acid, it was also observed that coumarin (I,A) reacted to yield the sulphonic acid which was found to be the same as the one obtained by oxidation of sulphinic acid (II), while no reaction took place on coumarin (I,B).

These results therefore suggest that in 6-hydroxycoumarin derivatives, position '5' is the only reactive position, and the failure of 4-methyl-6-hydroxycoumarin to react is probably due to steric effect of the methyl group on this position. Similar observations have been made in the Friedel-Crafts acylation of 6-hydroxycoumarin derivatives (Desai and Mavani, *Proc. Ind. Acad. Sci.*, 1942, **15A**, 1, 11 ; 1947, **25A**, 327 ; Thakor, *Curr. Sci.*, 1951, **20**, 234).

* Present address : D E. Society's Bombay College, Dadar, Bombay-28.

## EXPERIMENTAL

*6-Hydroxycoumarin-5-sulphinic Acid* (II).—Thionyl chloride (2.35 c.c.) was gradually added to an intimate mixture of 6-hydroxycoumarin (I,A, 2.5 g.) and powdered anhydrous aluminium chloride (6.2 g.) at room temperature and was left overnight. It was decomposed by adding HCl (10 c.c.) and crushed ice (total volume 75 c.c.). Original coumarin (unchanged) that separated was removed and the filtrate after scratching was kept in the refrigerator. The sulphinic acid slowly separated within 2 to 3 days. It was dried in vacuum, m.p. 150° (decomp.), yield 0.5 g. Additional amount of sulphinic acid (about 0.2 g.) was recovered from the filtrate, after concentrating it under reduced pressure. At first the original coumarin (pobably due to decomposition of sulphinic acid) that precipitated, was removed.

Pure sulphinic acid was obtained by acidifying the aqueous solution of crystallised potassium salt of sulphinic acid, m.p. 153° (decomp.). (Found : S, 14.66. $C_9H_6O_5S$ requires S, 14.16%). It developed a violet coloration with alcoholic ferric chloride.

*Potassium salt* was prepared by adding alcoholic potash to an alcoholic solution of sulphinic acid till a slight permanent yellow tinge appeared in the solution. It was crystallised from alcohol (with a few drops of water) as long needles.

*Ammonium salt* was prepared by passing dry ammonia gas in an alcoholic solution of the sulphinic acid and was crystallised from alcohol (with afew drops of water) in shining cubes. (Found : N, 5.38. $C_9H_{10}O_5NS$ requires N, 5.74%).

*s-Benzylisothiourea derivative* was prepared by adding an aqueous solution of *s*-benzyl*iso*thiourea hydrochloride to the aqueous solution of potassium salt of sulphinic acid. It was crystallised from alcohol as shining needles, m.p. 145° (decomp.). (Found : N, 7.60. $C_{17}H_{16}O_5N_2S_2$ requires N, 7.14%).

*6-Hydroxycoumarin-5-sulphonic Acid* (*Sodium salt*): (*i*) *Oxidation of Sulphinic Acid* (II).—The sulphinic acid (II; 0.5 g. in 5 c.c. of sodium bicarbonate solution) was oxidised by adding hydrogen peroxide (3 c.c. of 100 vol. + 7 c.c. of water), keeping first at room temperature for about 2 hours, and then heating on a water-bath for about an hour. The sulphonic acid was isolated as its sodium salt by adding a saturated solution of sodium chloride to the neutralised mixture after concentrating it to a small bulk. It separated as a crystalline solid. *s-Benzylisothiourea* derivative was prepared as usual. It was crystallised from water in prismatic crystals, m.p. 148-50°. (Found : N, 7.23. $C_{17}H_{16}O_6N_2S_2$ requires N, 6.86%).

(*ii*). *Sulphonation with Chlorosulphonic Acid.*—Chlorosulphonic acid (1.5 c.c.) was gradually added to 6-hydroxycoumarin (I,A; 1 g.) and the mixture was heated on a water-bath for about 2 hours. Crushed ice was added to it after cooling and a little pasty product that separated was removed. The filtrate was boiled to drive off HCl, when the unchanged coumarin separared. It was removed and the solution was concentrated to a small bulk and poured in the small quantity of saturated solution of common salt when sodium salt of the sulphonic acid slowly separated. *s-Benzylisothiourea derivative* was crystallised from water, m.p. and mixed m.p. with previous specimen, 148-50°.

*6 Hydroxy- 5 -chloromercuricoumarin.*—To the solution of the sulphinic acid (II ; 0.5 g. in 10 c.c. of absolute alcohol) a solution of mercuric chloride (1 g. in 10 c c. of alcohol) was added in cold and the mixture was well shaken. A crystalline solid slowly separated with continuous evolution of sulphur dioxide. It was kept for about 4 hours at room temperature and then filtered. It was purified by first boiling with water and then with alcohol as it was insoluble in most of the solvents. (Found : Hg, 49.9. $C_9H_5O_3HgCl$ requires Hg, 50.4%).

ORGANIC CHEMISTRY LABORATORIES,
THE INSTITUTE OF SCIENCE,
BOMBAY-1.

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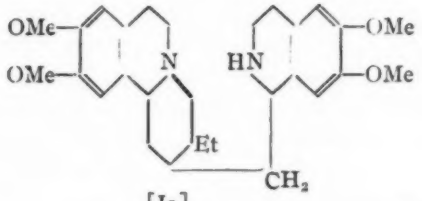
# POSSIBLE ANTIAMOEBIC AGENTS. PART VIII. SYNTHESIS OF DIALKYLAMINODIMETHYLENE-PHENYLETHYLAMINES

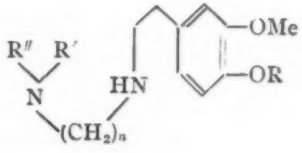
By A. B. Sen and S. L. Arora

Several substituted dialkylaminodimethylene-phenylethylamines, based on the partial structure of emetine, have been synthesised with a view to testing their antiamoebic activity.

It has been postulated by several workers (Pyman *et al.*, *Chem. & Ind.*, 1937, **55**, 789 ; Goodson and Goodwin, *Brit. J. Pharmacol.*, 1948, **3**, 44, 49, 62 ; Sugasawa, *J. Pharm. Soc., Japan*, 1949, **69**, 8; Osbond, *J. Chem. Soc.*, 1951, 3464) that the activity of emetine (Ia) is due to the presence of two nitrogen centres, of which one is secondary and the other is tertiary, separated by a carbon chain. Sen and Kulkarni (this *Journal*, 1958, **35**, 205) synthesised a number of dialkylaminotrimethylene-benzylamines and observed appreciable amoebacidal activity *in vitro* in this group of compounds. Encouraged by these observations several diamines (Ib), based on the partial structure of emetine, containing one secondary and another tertiary nitrogen atom with an intervening bridge of two carbon atoms, have been prepared with a view to studying their amoebacidal activity.



[Ia]



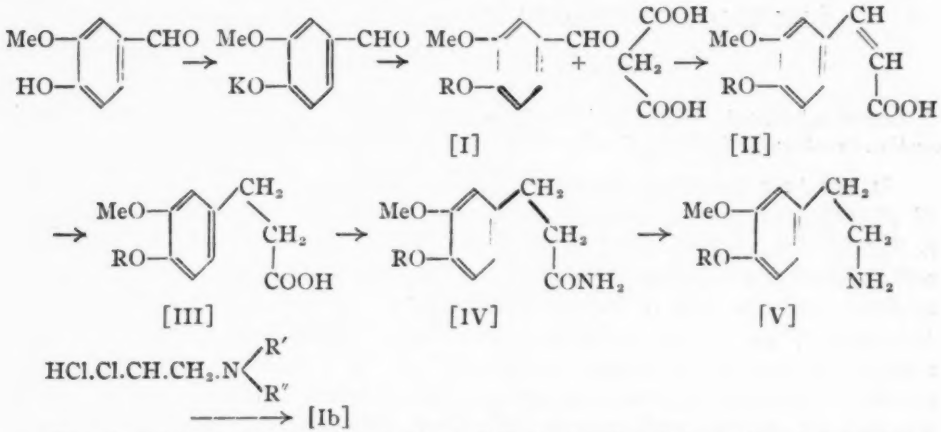
[Ib]

[Ib : R′ = R″ = piperidino or morpholino ; R = different alkyl groups ; $n = 2$].

The $\beta$-dialkylaminodimethylene-phenylethylamines (Ib) were prepared by the condensation of the appropriate dialkoxyphenylethylamines with dialkylaminoethyl chloride hydrochloride in absolute alcohol in the presence of anhydrous potassium carbonate (Kermack and Wight, *J. Chem. Soc.*, 1935, 1421).

Attempts to prepare the dialkoxyphenylethylamines by the reduction of the corresponding $\beta$-nitrostyrenes by Adams' catalyst did not succeed and these were therefore prepared by a five-step synthesis, starting from the appropriate dialkoxy-(3 : 4-dimethoxy-, 3-methoxy-4-*n*-butoxy-, 3-methoxy-4 *n*-amyloxy-, 3-methoxy-4-*n*-hexyloxy- and 3-methoxy-4-*n*-heptyloxy)-benzaldehydes. The alkoxybenzaldehydes (I) were obtained from vanillin by the action of different alkyl halides and were then converted into the corresponding cinnamic acids (II) by condensation with malonic acid in the presence of pyridine, which in turn were reduced to the corresponding hydrocinnamic acids (III) by sodium amalgam and water. The hydrocinnamic acids were then converted

into the corresponding amides (IV) via the acid chloride, followed by treatment with aqueous ammonia, and finally the amides were converted into the corresponding dialkoxyphenylethylamines (V) by the Hoffmann reaction. The various steps involved are :



The phenylethylamines (V) and the β-dialkylaminodimethylene-phenylethylamines (Ib) were characterised as their picrates.

## EXPERIMENTAL

*Dialkoxy-benzaldehydes* (I).—3 : 4-Dimethoxybenzaldehyde was prepared from vanillin and dimethyl sulphate in alkaline medium (Vogel, "Practical Org. Chem.", p. 804). The other dialkoxy-(3-methoxy-4-*n*-butoxy-, 3-methoxy-4-*n*-amyloxy-, 3-methoxy-4-*n*-hexyloxy- and 3-methoxy-4-*n*-heptyloxy)-benzaldehydes were obtained according to Dickinson *et al.* (*J. Chem. Soc.*, 1927, 1894). Vanillin (1*M*) was dissolved in 10% aqueous KOH (1*M*) solution, and evaporated to dryness on a water-bath. The K-salt of vanillin (1*M*) was then refluxed with the appropriate alkyl bromide (1.47*M*) in absolute alcohol over a steam-bath for 12 hours. The alcohol was removed by distillation and water was added to the residual mass, when an oily liquid separated out which was taken up in ether. The ethereal extract was dehydrated and distilled under reduced pressure, when the alkoxy-benzaldehydes were obtained in very good yields (cf. Pearl, *J. Amer. Chem. Soc.*, 1955, **77**, 757).

*Dialkoxy-cinnamic acids* (II) were prepared by heating the appropriate dialkoxybenzaldehyde (1*M*) with malonic acid (1.15*M*) in pyridine (250 c.c.) in the presence of piperidine (1 c.c.) on a water-bath for 4 to 6 hours, and then pouring the mass in cold 1 : 1-HCl, when the cinnamic acid separated out. This was filtered, washed with 1 : 1-HCl, then with water and finally dissolved in a saturated aqueous solution of $Na_2CO_3$ and reprecipitated with HCl, filtered, dried and recrystallised from alcohol or benzene (Slotta *et al.*, *Ber.*, 1930, **63**, 3036).

3 : 4-Dimethoxycinnamic acid has been reported by Perkin *et al.* (*J. Chem. Soc.*, 1924, 1679), 3-methoxy-4-*n*-butoxy- and 3-methoxy-4-*n*-hexyloxy-cinnamic acids have been reported by Moore *et al.* (*J. Amer. Chem. Soc.*, 1954, **76**, 3656).

The yields, m.p., neutralisation equivalents and the analysis of the other two acids are recorded in Table I.

TABLE I

| Dialkoxy-cinnamic acids. | M.P. | Yield. | Neut. equiv. Found. | Neut. equiv. Calc. | % Carbon. Found. | % Carbon. Calc. | % Hydrogen. Found. | % Hydrogen. Calc. |
|---|---|---|---|---|---|---|---|---|
| 3-Methoxy-4-*n*-amyloxy- | 118° | 91% | 263.9 | 264 | 68.10 | 68.20 | 7.60 | 7.57 |
| 3-Methoxy-4-*n*-heptyloxy- | 132° | 85 | 292.1 | 292 | 69.70 | 69.85 | 8.30 | 8.21 |

*Dialkoxy-hydrocinnamic acids* (III) were obtained by the reduction of the appropriate cinnamic acids with sodium amalgam and water according to Erlenmeyer *et al.* (*Annalen*, 1862, **121**, 375; 1866, **137**, 237). The appropriate cinnamic acid (0.1*M*) was taken in ten times its weight of water in a three-necked flask fitted with an efficient stirrer, and made alkaline by adding an equivalent amount of NaOH. In the case of 3-methoxy-4-*n*-heptyloxy-cinnamic acid, alcohol (95%) was added to the alkaline suspension in order to bring the acid in solution. The alkaline solution of the acid was stirred vigorously and 251.6 g. of sodium amalgam (3%) was added portionwise during 4 hours at room temperature. The stirring was continued for another 4 hours after which it was cooled and acidified with HCl (conc.), when the hydrocinnamic acid precipitated out which was filtered, washed with cold water, dried and recrystallised either from alcohol or benzene.

3:4-Dimethoxyhydrocinnamic acid has been reported by Perkin *et al.* (*J. Chem. Soc.*, 1907, 1079), while 3-methoxy-4-*n*-butoxy- and 3-methoxy-4-*n*-hexyloxy-hydrocinnamic acids have been reported by Moore *et al.* (*loc. cit.*).

The yields, m.p., neutralisation equivalents and the analyses of the other acids are recorded in Table II.

TABLE II

| Dialkoxy-hydrocinnamic acids. | M.P. | Yield. | Neut. equiv. Found. | Neut. equiv. Calc. | % Carbon. Found. | % Carbon. Calc. | % Hydrogen. Found. | % Hydrogen. Calc. |
|---|---|---|---|---|---|---|---|---|
| 3-Methoxy-4-*n*-amyloxy- | 69° | 94% | 266.1 | 266 | 67.70 | 67.67 | 8.25 | 8.27 |
| 3-Methoxy-4-*n*-heptyloxy- | 76° | 96 | 293.9 | 294 | 69.30 | 69.40 | 8.80 | 8.84 |

*Dialkoxy-phenylpropionamides* (IV) were prepared according to Pictet *et al.* (*Ber.*, 1909, **42**, 1985) by dissolving the appropriate hydrocinnamic acid (0.1*M*) in dry $CHCl_3$, adding $PCl_5$ (0.1*M*) under cooling and finally refluxing on the water-bath till HCl fumes had ceased to evolve. The $CHCl_3$ and $POCl_3$ were removed under reduced pressure. The acid chloride, thus obtained, was cooled and aqueous ammonia was added in small lots with vigorous shaking till ammonia was in excess. The amide separated out as a solid, which was recrystallised either from benzene or benzene-petroleum ether mixture.

3:4-Dimethoxyphenylpropionamide has been reported by Pictet *et al.* (*loc. cit.*). The yields, m.p., and the analyses of the alkoxy-phenylpropionamides are recorded in Table III.

TABLE III

| Dialkoxy-phenyl-propionamides. | M.P. | Yield. | % Nitrogen. Found. | % Nitrogen. Calc. | % Carbon. Found. | % Carbon. Calc. | % Hydrogen. Found. | % Hydrogen. Calc. |
|---|---|---|---|---|---|---|---|---|
| 3-Methoxy-4-*n*-butoxy- | 112° | 70% | 5.50 | 5.57 | 66.90 | 66.93 | 8.30 | 8.36 |
| 3-Methoxy-4-*n*-amyloxy- | 97° | 55 | 5.28 | 5.28 | 67.80 | 67.99 | 8.70 | 8.68 |
| 3-Methoxy-4-*n*-hexyloxy- | 101° | 54 | 5.10 | 5.01 | 68.90 | 68.81 | 9.00 | 8.96 |
| 3-Methoxy-4-*n*-heptyloxy- | 96° | 82 | 4.82 | 4.77 | 69.50 | 69.61 | 9.30 | 9.21 |

*Dialkoxy-phenylethylamines* (V) were prepared according to Woodruff *et al.* (*J. Amer. Chem. Soc.*, 1938, **60**, 465) by adding the appropriate amide (0.1*M*) to a solution of bromine (0.106*M*), dissolved in 10% KOH solution (4 *M*), cooled to 0°. The solution was stirred till most of the amide went into solution; it was then filtered and the filtrate heated for 2 hours at 70-80°. Solid NaOH (16 g.) was then added and the heating was continued at 80° for another 2 hours, when the amine separated out as an oil. After cooling the reaction mixture, the amine was taken up in ether, the ether extract dried (anhydrous magnesium sulphate), the ether removed and the residue distilled under reduced pressure.

Out of the five phenylethylamines prepared, 3 : 4 dimethoxyphenylethylamine has been reported by Mannich *et al.* (*Ber.*, 1910, **43**, 196).

The yields, boiling points, and analyses of the other phenylethylamines and their picrates are recorded in Table IV.

TABLE IV

| Dialkoxy-phenylethylamines. | Amines. B.P. | Amines. % Yield. | Amines. % Nitrogen. Found. | Amines. % Nitrogen. Calc. | Picrates. M.P. | Picrates. % Nitrogen. Found. | Picrates. % Nitrogen. Calc. |
|---|---|---|---|---|---|---|---|
| 3-Methoxy-4-*n*-butoxy | 145/10 mm | 84 | 6.30 | 6.27 | 101° | 12.30 | 12.40 |
| 3-Methoxy 4-*n*-amyloxy- | 180/10 | 74 | 5.30 | 5.90 | 115° | 12.00 | 12.02 |
| 3-Methoxy-4-*n*-hexyloxy- | 160/10 | 70 | 5.58 | 5 57 | | | |
| 3-Methoxy-4-*n*-heptyloxy- | 170/10 | 75 | 5.30 | 5.28 | | | |

*Dialkyl-aminoethyl chloride hydrochlorides* were prepared according to Kermack and Wight (*loc. cit.*), as described below.

4-*Morpholinoethanol.*—Morpholine (34.84 g., 0.4*M*) was added to a solution of ethylenechlorohydrin (16.1 g., 0.2*M*) in dry benzene (100 c.c.) and the mixture was refluxed for 10 hours. It was then cooled in ice, when the morpholine hydrochloride separated out. It was removed by filtration. After removing the benzene from the filtrate, the residual liquid was distilled, when 4-morpholinoethanol distilled, b.p. 220-23°, yield 25 g. (95% of the theory).

1-*Piperidienoethanol* was obtained similarly from piperidine (34 g., 0.4*M*) and ethylenechlorohydrin (16.10 g., 0.2*M*) in dry benzene, b.p. 197-98°, yield 23 g. (89% of the theory).

## TABLE V

(Vide structure Ib)

| R. | R′ & R″. | Diamines. B. P. | %Yield. | Mol. formula. | %Nitrogen. Found. | %Nitrogen. Calc. | Picrates. M.P. | Mol. formula. | %Nitrogen. Found. | %Nitrogen. Calc. |
|---|---|---|---|---|---|---|---|---|---|---|
| Methoxy- | Piperidyl- | 126-28°/8 mm | 74.5 | $C_{17}H_{28}O_2N_2$ | 9.50 | 9.59 | 196° | $C_{29}H_{31}O_{16}N_8$ | 14.70 | 14.93 |
| 4-*n*-Butoxy- | ,, | 168°/ | 66.6 | $C_{20}H_{34}O_2N_2$ | 8.40 | 8.38 | 178° | $C_{32}H_{40}O_{16}N_8$ | 14.00 | 14.14 |
| 4-*n*-Amyloxy- | ,, | 142°/ | 81.6 | $C_{21}H_{36}O_2N_2$ | 8.00 | 8.04 | 172° | $C_{33}H_{42}O_{16}N_8$ | 13.80 | 13.90 |
| 4-*n*-Hexyloxy- | ,, | 145°/ | 40 | $C_{22}H_{38}O_2N_2$ | 7.82 | 7.74 | | | | |
| 4-*n*-Heptyloxy- | ,, | 160°/ | 50 | $C_{23}H_{40}O_2N_2$ | 7.40 | 7.45 | | | | |
| Methoxy- | Morpholinyl- | 120°/ | 50 | $C_{16}H_{26}O_3N_2$ | 9.48 | 9.53 | 209° | $C_{28}H_{32}O_{17}N_8$ | 14.62 | 14.89 |
| 4-*n*-Butoxy- | ,, | 160°/ | 60 | $C_{19}H_{32}O_3N_2$ | 8.20 | 8.33 | 184° | $C_{31}H_{38}O_{17}N_8$ | 13.90 | 14.12 |
| 4-*n*-Amyloxy- | ,, | 155°/ | 52 | $C_{20}H_{34}O_3N_2$ | 7.88 | 8.00 | 152° | $C_{32}H_{40}O_{17}N_8$ | 13.62 | 13.80 |

*4-Morpholinoethyl Chloride Hydrochloride.*—4-Morpholinoethanol (13.1 g., 0.1*M*) was taken in dry benzene (100 c.c.) in a three-necked flask which was cooled externally by ice. After cooling, thionyl chloride (0.12*M*) was added dropwise during 2½ hours. The reaction mixture was then heated on a water-bath at 60-70° for another 3 hours. It was then cooled and the chloride hydrochloride separating was recrystallised from acetone, m.p. 180°, yield 17.3 g. (93% of theory).

*1-Piperidinoethyl chloride hydrochloride* was obtained in the same way from 1-piperidinoethanol (12.9 g., 0.1*M*) and thionyl chloride (0.12*M*), m.p. 226°, yield 16.2 g. (88% of theory).

*β-Dialkylaminodimethylene-phenylethylamines* (Ib) were prepared according to Kermack and Wight (*loc. cit.*). The appropriate dialkylaminoethyl chloride hydrochloride (0.01*M*), anhydrous potassium carbonate (0.01*M*) and absolute alcohol (13-15 c.c. for every 2.5 g. of the hydrochloride) were taken in a r.b. flask fitted with a dropping funnel and a condenser, and cooled externally by ice ; then the appropriate phenylethylamine (0.01*M*) was added with shaking. The mixture was refluxed on a steam-bath for 6 to 7 hours, cooled and diluted with water, when the liquid diamine separating out was removed and the aqueous layer left was saturated with sodium chloride and extracted twice with ether. The ether extract was added to the diamine and after drying over anhydrous potassium carbonate it was filtered, the solvent removed and the residual liquid distilled under reduced pressure. The diamines were characterised as their picrates.

*Picrates.*—Hot alcoholic solutions of the amine (0.2 g.) and picric acid (0.2 g.) were mixed and heated on a steam-bath for 5 minutes, when yellow crystalline picrate separated out. The yields, boiling points, analyses of the diamines (Ib) and their picrates are recorded in Table V.

CHEMICAL LABORATORY,
LUCKNOW UNIVERSITY,
LUCKNOW.

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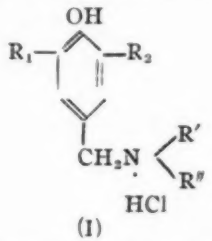
# POSSIBLE ANTIAMOEBIC AGENTS. PART IX. SYNTHESIS OF MANNICH BASE HYDROCHLORIDES OF SUBSTITUTED PHENOLS

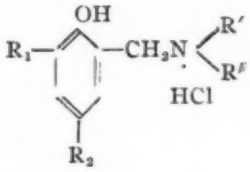
By A. B. Sen and O. P. Madan

Several Mannich base hydrochlorides have been synthesised from substituted phenols with a view to testing their antiamoebic activity.

Sen and Arora (this *Journal*, 1958, **35**, 613) reported the synthesis of a number of compounds based on the partial structure of camoform, an effective amoebacide introduced by Parke Davis & Co. These compounds have been found to possess antiamoebic activity more than camoform, when tested *in vitro*. The present work reports the synthesis of Mannich base hydrochlorides (I & II) from unsaturated phenols containing different alkyl and halogen groupings (allyl, amyl$^t$, butyl$^t$, methyl and chloro), with a view to studying their antiamoebic activity.




(I)




(II)

[$R_1$ & $R_2$ : substituents in the nucleus ; R′ & R″ : substituents in the basic side chain]

The allylphenols were prepared by the Claisen rearrangement of the corresponding allylphenyl ethers.

Mannich base hydrochlorides were prepared from 2-allyl-4-amyl$^t$-, 2-allyl-6-methyl-, 2-allyl-6-chloro-, 2 : 6-diallyl- and 2-chloro-4-butyl$^t$-phenols, using formaldehyde and different amines (piperidine, morpholine, piperazine and benzylamine), following the method of Bruson *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 270). The bases were characterised as their picrates ; stability was examined in aqueous solution.

## Experimental

*Substituted Allylphenols.*—2-Allyl-4-amyl$^t$-(Sen and Rastogi, this *Journal*, 1953, **30**, 556), 2-allyl-6-methyl-(Claisen and Eisleb, *Annalen*, 1913, **401**, 79), 2 : 6-diallyl-(Claisen, *ibid.*, 1919 **418**, 97), and 2-allyl-6-chloro-phenols (Tarbell and Wilson, *J. Amer. Chem. Soc.*, 1942, **64**, 1070) were prepared by the methods given in literature.

TABLE I

| Sl. No. | R′ & R″. | Mannich base hydrochlorides. M.P. | % Yield. | Formula. | % Nitrogen. Found. | Calc. | Picrates. M.P. | Formula. | % Nitrogen. Found. | Calc. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $R_1$ & $R_2$ = 2-Allyl-4-amyl'-. | | | | | | | | |
| 1. | Piperidyl- | 195° | 78 | $C_{20}H_{32}ONCl$ | 4.01 | 4.14 | ... | ... | ... | ... |
| 2. | Morpholinyl- | 195° | 96 | $C_{19}H_{30}O_2NCl$ | 4.20 | 4.12 | ... | ... | ... | ... |
| 3. | Piperazine | 216° | 54 | $C_{34}H_{54}O_2N_2Cl_2$ | 4.42 | 4.73 | 194° | $C_{46}H_{53}O_{16}N_8$ | 11.25 | 11.45 |
| | | $R_1$ & $R_2$ = 2-Allyl-6-methyl-. | | | | | | | | |
| 4. | Piperidyl- | 183° | 40 | $C_{16}H_{24}ONCl$ | 4.69 | 4.97 | ... | ... | ... | ... |
| 5. | Morpholinyl- | 199° | 95 | $C_{15}H_{22}O_2NCl$ | 4.92 | 4.93 | 152-53° | $C_{21}H_{24}O_9N_4$ | 11.61 | 11.70 |
| | | $R_1$ & $R_2$ = 2-Allyl-6-chloro-. | | | | | | | | |
| 6. | Piperidyl- | 168-70° | 57 | $C_{15}H_{21}ONCl_2$ | 4.31 | 4.63 | ... | ... | ... | ... |
| 7. | Morpholinyl- | 163° | 67 | $C_{14}H_{19}O_2NCl_2$ | 4.42 | 4.60 | ... | ... | ... | ... |
| 8a. | Piperazine | 161° | 50 | $C_{34}H_{38}O_2N_2Cl_2$ | 6.42 | 6.26 | * 259° | $C_{36}H_{34}O_{16}N_8Cl_2$ | 12.06 | 12.37 |
| 8b. | ,, | *204° | ... | $C_{24}H_{36}O_2N_2Cl_4$ | 5.11 | 5.38 | ... | ... | ... | ... |
| 9. | Benzyl- | 189° | 63 | $C_{17}H_{19}ONCl_2$ | 4.17 | 4.32 | 116-17° | $C_{23}H_{21}O_8N_4Cl$ | 10.60 | 10.86 |
| | | $R_1$ & $R_2$ = 2 :6-Diallyl-. | | | | | | | | |
| 10. | Piperidyl- | 173° | 30 | $C_{18}H_{26}ONCl$ | 4.38 | 4.55 | ... | ... | ... | ... |
| 11. | Morpholinyl- | 158° | 63 | $C_{17}H_{24}O_2NCl$ | 4.47 | 4.52 | 154-55° | $C_{23}H_{26}O_8N_4$ | 11.34 | 11.52 |
| 12. | Piperazine | *232° | 32 | $C_{30}H_{40}O_2N_2Cl_2$ | 4.91 | 5.27 | ... | ... | ... | ... |
| 13. | Benzyl- | 168° | 53 | $C_{20}H_{24}ONCl$ | 3.95 | 4.42 | ... | ... | ... | ... |
| | | $R_1$ & $R_2$ = 2-Chloro-4-butyl'-. | | | | | | | | |
| 14. | Piperidyl- | 226° | 47 | $C_{16}H_{25}ONCl_2$ | 4.04 | 4.40 | 190° | $C_{22}H_{27}O_8N_4Cl$ | 10.62 | 10.97 |
| 15. | Morpholinyl- | 128° | 60 | $C_{15}H_{23}O_2NCl_2$ | 4.21 | 4.37 | 151-52° | $C_{21}H_{26}O_9N_4Cl$ | 10.75 | 10.92 |
| 16a. | Piperazine | 261° | 64 | $C_{26}H_{36}O_2N_2Cl_2$ | 5.72 | 5.87 | ... | ... | ... | ... |
| 16b. | ,, | *265° | ... | $C_{26}H_{38}O_2N_2Cl_4$ | 4.18 | 4.29 | ... | ... | ... | ... |
| 17. | Benzyl- | 213° | 91 | $C_{18}H_{23}ONCl_2$ | 4.02 | 4.00 | ... | ... | ... | ... |

Note : a– as free Mannich base ; b–the hydrochlorides of the Mannich base.

*Compounds melt with decomposition.

*Mannich Base Hydrochlorides.*—To a mixture of the substituted phenol (0.01 *M*) and the amine (0.013 *M*), cooled in ice, was added dropwise, with shaking, in about 30 minutes, the calculated amount (0.01 *M*) of a 30% solution of formaldehyde, when a thick emulsion was obtained. The reaction mixture after keeping at room temperature for ½ hour was refluxed on a water-bath for 2 hours, when an oily layer soon separated out. To this was added pure sodium chloride (2 g.) and the mixture was further refluxed for ½ hour. After cooling, the oily layer was extracted with ether and the extract dried ($MgSO_4$). Dry HCl gas was passed in the cold ether extract, when the Mannich base hydrochloride separated out. It was recrystallised from absolute alcohol or benzene as required.

In the case of No. 8a and 16a (Table I), Mannich bases separated as crystalline solids after a few minutes of refluxing. These were redissolved by adding absolute alcohol and further refluxed for 2 hours.

*Picrates.*—The Mannich base hydrochlorides (0.2 g. each) (No. 3,5, 8a, 9, 11, 14 and 15 in Table I) were dissolved in cold rectified spirit (5 c.c.) and to this was added a cold alcoholic saturated solution of picric acid (5 c.c.), and warmed on a water-bath for 5 minutes. On cooling the picrates separated out, which were recrystallised from alcohol.

*Stability.*—The compounds (No. 2, 3, 4, 5, 9, 11 and 14 in Table I) (0.2 g. each) were dissolved in water (5 c.c.) separately and kept at room temperature for 40 hours. The solutions remained transparent throughout. On evaporating the aqueous solutions on the water-bath, the original compounds were recovered except in the case of No. 3 and 4. A depression of melting points was observed in these two cases, indicating decomposition.

The melting points, yields and analysis of Mannich base hydrochlorides and their picrates are recorded in Table I.

CHEMICAL LABORATORIES,
LUCKNOW UNIVERSITY,
LUCKNOW.

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# GENIN-A AND *ISO*RHAMNETIN FROM THE BARK OF *AEGICERAS MAJUS* GAERTN*

By K. Venkateswara Rao and P. K. Bose

Genin-A and *iso*rhamnetin (quercetin 3′-methyl ether) have been isolated from the bark of *Aegiceras majus* Gaertn.

*Aegiceras majus* Gaertn (Syn. *A. corniculatum* Blanco) of the family Myrsinaceae, is a shrub or small tree, commonly met with in the mangrove swamps of Asia and Australia. The bark is used as a fish poison. Although the presence of a saponin, $C_{22}H_{36}O_{10}$, was reported by Weiss (*Arch. Pharm.*, 1906, **244**, 221) in the fruit and bark of the plant, the aglycone has only recently been isolated by Kinel and Gedeon (*ibid.*, 1956, **289**, 221) who considered it to be a new saturated triterpene of molecular formula $C_{30}H_{52}O_3$ and suggested the name Kanjalagin. The latter also recorded a m.p. 230-32°, $[\alpha]_D$ + 42°.5 ($CHCl_3$) for the sapogenin and for its unanalysed acetate, a m.p. of 330-40°. It appeared therefore that this might prove to be the first instance of a saturated triterpene occurring in nature as a saponin, and hence we undertook a re-investigation of the bark.

Alcohol extraction of the defatted bark gave a large amount of saponin from which by acid hydrolysis and subsequent take-up with benzene, a mixture of triterpene mono-, di- and tri-ols was obtained. The compound, closely agreeing with Kanjalagin in physical properties and m.p., was isolated from this mixture by chromatography and further purified through its acetate. The pure sapogenin had m.p. 243-45°, $[\alpha]_D^{32}$ + 29°.4 (absolute ethanol) and analysed for $C_{30}H_{50}O_3$, while its triacetate melted at 158-59° ; $[\alpha]_D^{31}$ − 9°.2 ($CHCl_3$). The acetate showed an intense yellow colour with tetranitromethane and in contrast to the finding of the earlier workers, the sapogenin exhibited a faint but distinct yellow colour with this reagent. It is possible that the use of a dilute solution of the sapogenin, in view of its sparing solubility in chloroform, might have led them to think that the compound was fully saturated. Eventually it was identified as genin-A {lit. m.p.* **249.5-50°, $[\alpha]_D$ + 52° ($CHCl_3$) ; triacetate, m.p. 159-60°, $[\alpha]_D$ − 10° ($CHCl_3$). Also a m.p. 248-50°, $[\alpha]_D$ +. 32°.8 ± 2 (absolute ethanol) for genin-A †} by determination of mixed m.p. with an authentic sample, prepared by the lithium aluminium hydride reduction of the methyl ester of echinocystic acid isolated in this laboratory (Barua and Raman, *Science & Culture*, 1958, **23**, 435).

Ether extraction of the crude sapogenin, after removal of the triterpenoids with benzene, yielded a flavonol, $C_{16}H_{12}O_7$, m.p. 300° (decomp.). Its homogeneity was established by paper chromatography which gave a single spot in two different solvent systems. It contains one methoxyl group. On demethylation under Zeisel's conditions,

* Abstracts of the paper have been published in Proc. Indian Sci. Congress, 1958, Part III, p. 174 and 1959, Part III, p. 137.

** Jeger, Nisoli and Ruzicka, *Helv. Chim. Acta*, 1946, **29**, 1183.

† Paech and Tracy, "Modern Methods of Plant Analysis", 1955, Vol. III, p. 99.

it furnished quercetin, characterised through its acetate ; on complete methylation, quercetin pentamethyl ether was obtained. It formed a tetra-acetate, m.p. 208-209°. These values agree well with those recorded for *iso*rhamnetin [Heilbron and Bunbury, "Dictionary of Organic Compounds", 1953, Vol. 3, p. 125, record m.p. 305° (d) ; acetate m.p. 205-207°]. The flavonol acetate showed no depression in m.p. on admixture with an authentic sample of *iso*rhamnetin tetra-acetate. The spectrophotometric evidence also favours the above conclusion. The failure of the long wave-length maximum of the flavonol to shift in the presence of alcoholic boric acid-sodium acetate shows the absence of *o*-dihydroxyl group in it. It may be pointed out that quercetin under these conditions shows a bathochromic shift of 16 mμ (Jurd, *Arch. Biochem. & Biophys.*, 1956, **63**, 376). As no free flavonol could be located in the plant it may be presumed to be present as a glycoside.

## *EXPERIMENTAL

*Isolation of Genin-A.*—The powdered bark (1 kg.) was extracted successively with petroleum (b.p. 60-80°), chloroform and ethanol (95%). The alcoholic extract was distilled under reduced pressure and the residue, responding to the tests for saponin, was taken up with minimum amount of water and extracted repeatedly with hot ethyl acetate. The saponin was then hydrolysed under reflux for 4 hours with aqueous alcohol (1 : 1 ; 1 litre) and HCl (conc.. 200 c.c.). The crude sapogenin was collected, washed, dried and soxhleted with benzene and then with ether.

The benzene fraction on concentration to *ca.* 150 c.c. yielded a colorless solid (6.5 g.) which on dissolution in ether and washing with alkali afforded no acidic fraction. It had an extended m.p. of 220-235°. Chromatography of its solution in benzene-ether (1 : 1) over neutral alumina and elution with the same solvent, followed by crystallisation from aqueous ethanol, raised the m.p. of the sapogenin to 235-38°. It developed, in the Liebermann-Burchard test, a rose colour changing to pink.

*Genin-A Triacetate.*—The sapogenin was acetylated with an excess of acetic anhydride and pyridine on the steam-bath for 3 hours, left overnight, and worked up in the usual way. Chromatography of a solution of the acetate in light petroleum-benzene (3:1) over neutral alumina and elution with the same solvent, yielded a gum which on crystallisation from methanol furnished genin A triacetate as colorless needles, m.p. and mixed m.p. 158-59°, $[\alpha]_D^{31}$ − 9°.2 (*c*, 5.54 in $CHCl_3$). (Found : C 73.64 ; H, 9.42. $C_{36}H_{56}O_6$ requires C, 73.97 ; H, 9.59%). It developed an intense yellow colour with tetranitromethane.

*Hydrolysis of the Acetate.*—Hydrolysis of the above acetate with ethanolic potassium hydroxide and chromatography of the residue in benzene-ether (1 : 1) over neutral alumina and elution with the same solvent provided a fraction of m.p. 240-42°, which on further crystallisations from chloroform-methanol melted at 243-45° ; $[\alpha]_D^{32}$ + 29°.4 (*c*, 0.88 in absolute ethanol). The m.p. remained undepressed on admixture with an authentic sample of genin-A. A saturated solution of the sapogenin in chloroform showed a yellow colour with tetranitromethane. (Found : C, 78.56 ; H, 10.86. $C_{30}H_{50}O_3$ requires C, 78.60 ; H, 10.91%).

* All m.p.s are uncorrected.

*Isolation of* iso*Rhamnetin*.—The ether extract of the crude sapogenin on evaporation to dryness left a residue which was triturated with ethyl acetate and the yellow solid (150 mg.) was filtered off. It was sparingly soluble in ethanol but crystallised from aqueous pyridine as yellow microscopic needles, m.p. 300° (decomp.). With magnesium and alcoholic hydrochloric acid it developed an orange-pink colour. It showed a dirty green colour with alcoholic ferric chloride solution and dissolved in aqueous sodium carbonate and hydroxide as also in dilute ammonia to provide yellow solutions, but it was insoluble in concentrated hydrochloric acid. (Found : C, 60.58 ; H, 4.01 ; OMe, 9.2. $C_{16}H_{12}O_7$ requires C, 60.76 ; H, 3.8 ; OMe, 9.8%).

Absorption (in ethanol) : $\lambda_{max}$ 255 m$\mu$ (log $\epsilon$ 4.36) and 375 m$\mu$ (log $\epsilon$ 4.38).

Absorption (with ethanolic boric acid-sodium acetate) : $\lambda_{max}$ 255 m$\mu$ (log $\epsilon$ 4.40) and 375 m$\mu$ (log $\epsilon$ 4.32).

$R_f$ value 0.80 (*n*-butanol-acetic acid-water, 4 : 1 : 1) and 0.72 (phenol-saturated water). Wada (*J. Amer. Chem. Soc.*, 1956, **78**, 4725) records for *iso*rhamnetin the $R_f$ values 0.83 and 0.71 respectively in the above solvent systems.

*Quercetin Pentamethyl Ether*.—The flavonol was methylated with excess dimethyl sulphate and anhydrous potassium carbonate in acetone medium. The product on crystallisation from aqueous methanol and then benzene-hexane furnished colorless needles, m.p. and mixed m.p. with quercetin pentamethyl ether, 151-52°. (Found : C, 64.52 ; H, 5.25. Calc. for $C_{20}H_{20}O_7$ : C, 64.51 ; H, 5.30%).

*Demethylation to Quercetin*.—The flavonol was heated for 3 hours at 150-60° with hydroiodic acid and phenol in an atmosphere of carbon dioxide. The yellow precipitate, formed on pouring the mixture into water, was directly acetylated. The acetate crystallised from ethanol as microscopic needles, m.p. and mixed m.p. with quercetin penta-acetate, 190-91°.

iso*Rhamnetin Tetra-acetate*.—The acetate of the flavonol, prepared in the usual way, was crystallised from ethanol as colorless microscopic needles, m.p. 208-209°, undepressed on admixture with an authentic sample of *iso*rhamnetin tetra-acetate, m.p. 203-204°. (Found : C, 59.34 ; H, 4.12. Calc. for $C_{24}H_{20}O_{11}$ : C, 59.5 ; H, 4.13%).

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CHEMISTRY DEPARTMENT,
BOSE INSTITUTE, CALCUTTA 9.

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# THE DECOMPOSITION OF ORGANIC COMPOUNDS*

E. W. R. STEACIE

NATIONAL RESARCH COUNCIL OF CANADA, OTTAWA, CANADA

In systematizing our knowledge of the chemical reaction of inorganic compounds the fundamental quantities are the heat of reaction and the free energy change. From a knowledge of the heats and free energies of formation of a relatively small number of the more important inorganic compounds it is possible to predict the position of equilibrium in a large number of reactions. Further, in inorganic reactions the equilibrium is the important thing, since it is usually attained with extreme rapidity. In the case of organic reactions the situation is quite different. Most organic compounds are intrinsically unstable, and the important thing is not the position of equilibrium, but the rate at which it is attained. Any generalisations which can be made about the rate of decomposition of organic compounds are therefore of great importance. Especially in the gas phase, it has been possible to make considerable progress in the last thirty years, and in particular the importance of short-lived intermediates (atoms and free radicals) in most gas-phase reactions has become evident during this period.

The transitory existence of free radicals and atoms has long been established in spectroscopy. Examples are OH, H, CH and $C_2$ and in recent years the methyl radical, $CH_3$, and many others. There is no question that the lack of existence of free radicals under ordinary circumstances is not due to any intrinsic substance of stability but rather to their high reactivity which results in their rapid disappearance by reaction with themselves or with other substances which may be present.

Thus of the possible hydrides of carbon :

$CH_5$
$CH_4$
$CH_3$
$CH_2$
CH,

$CH_5$ does not exist because it is intrinsically unstable. $CH_3$, $CH_2$ and CH, however, are about as stable as $CH_4$, if isolated, but do not normally exist because of rapid reactions to form $C_2H_6$, etc.

The idea that reactions involving free atoms may be of importance in chemical mechanisms first came from photochemistry. Once the significance of the Einstein law of photochemical equivalence was recognized, it became apparent that some sort of chain mechanism must be responsible for the very large quantum yields of reactions such as the photochemical synthesis of hydrogen chloride from hydrogen and chlorine.

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The so-called Nernst chain was the first case in which such atomic elementary reactions were seriously suggested. This was based on the idea that the initial action of light on chlorine was to split the molecule into chlorine atoms which then set up reaction chains by the mechanism:

$$Cl_2 + h\nu \longrightarrow 2Cl$$
$$Cl + H_2 \longrightarrow HCl + H$$
$$H + Cl_2 \longrightarrow HCl + Cl$$

It soon became evident that such atomic reactions had wide importance in photochemistry. In the 1920's it also became evident that free radicals such as methyl played a part in photochemical reactions and there were sporadic suggestions of their participation in thermal reactions.

Following on this work it was shown by Paneth in 1929 that free methyl radicals formed by the thermal decomposition of lead tetramethyl could be detected by their reaction with a metallic mirror deposited on the walls of a tube through which a carrier gas together with the radicals was flowing. This work proved conclusively that methyl and ethyl radicals were capable of existence for an appreciable fraction of a second at room temperature and low pressures. Subsequent work by Rice showed that free radicals could be detected in the thermal decomposition of a large number of organic compounds.

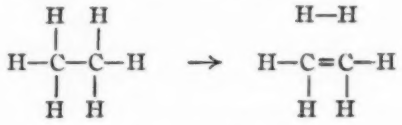
The detection of any chemical species is always a matter of some ambiguity and is always tainted with inference. It may, therefore, be noted that in spite of the very great historical significance of Paneth's work the existence of radicals is today much more certainly established by well-understood photochemical mechanisms than by the rather erratic results of mirror removal. In any case detection is today no longer a question of major importance as far as free radicals in the gas phase are concerned. The self-consistency of much photochemical and thermal evidence is the best guarantee of the existence and identity of radicals. The establishment of such mechanisms has been aided by a number of relatively new techniques. Among these are flash photolysis which produces very high radical concentrations, the trapping of radicals in solid matrices, mass spectrometry of free radicals and the detection of many polyatomic radicals by absorption spectroscopy. The most important cases of detection of radicals in recent years have been those of the methyl radical by absorption spectroscopy and of $HO_2$ by mass spectrometry.

Since Rice had found that radicals could be detected in most thermal decompositions, he suggested that most organic compounds decomposed by a free radical chain mechanism. While there is some uncertainty as to the exact mechanism involved, there is no question today, that free radicals play an important part in gas phase organic decompositions. As an example we may consider the decomposition of a simple organic compound such as ethane. The overall reaction is

$$C_2H_6 = C_2H_4 + H_2.$$

It should be emphasized, however, that this is merely a stoichiometric equation and has nothing to do with the mechanism of the reaction.

There are two main types of mechanism by which the decomposition might proceed. One of these is a direct intramolecular change, as indicated by the above equation, whereby a molecule of ethane forms a molecule of ethylene and one of hydrogen in a single step. If the reaction proceeded by one step in this way it would be simple from a mechanism point of view since only one step is involved, but would be a rather complex act from a molecular point of view since it would involve the more or less simultaneous breaking of two C—H bonds, the forming of an H—H bond and the conversion of a single C—C bond to a double bond.



Rice has suggested a free radical mechanism for the reaction in which the whole overall process is complicated and involves a variety of stages, but in which each of the stages is a relatively simple process, viz:

$$C_2H_6 \longrightarrow 2CH_3 \quad \ldots \quad \ldots \quad \ldots \quad (1)$$

$$CH_3 + C_2H_6 \longrightarrow CH_4 + C_2H_5 \quad \ldots \quad \ldots \quad (2)$$

$$C_2H_5 \longrightarrow C_2H_4 + H \quad \ldots \quad \ldots \quad (3)$$

$$H + C_2H_6 \longrightarrow H_2 + C_2H_5 \quad \ldots \quad \ldots \quad (4)$$

etc.

Thus the first reaction involves the simple split of a single C—C bond. Reaction (3) involves again a split of one bond, but in this case reorganization of the resulting biradical to ethylene must occur. Reactions (2) and (4) involve the simplest possible metathesis in which one atom wanders from one reactant to the other.

The main feature of the mechanism is that the H-atom lost by (4) is regenerated by (3). Thus (3) and (4) together constitute a reaction chain which can repeat over and over again, and one molecule of ethane disappears and one each of ethylene and of hydrogen are formed in each cycle. The complex scheme thus yields the right final products.

It follows that whenever an ethane molecule decomposes by (1) to give two methyl radicals, a chain is set up and many molecules of ethane decompose. The relative importance of a molecular rearrangement or a free radical mechanism will depend on two factors: the relative activation energies and steric factors of the two reactions, and the length of the chain.

In general, it will be a tidier process to split a bond in the molecule, rather than have it undergo a complex rearrangement, but it will involve a greater energy input. Thus the simplest scheme would be to pull all the atoms apart and put them together again,

$$C_2H_6 \longrightarrow 2C + 6H$$

$$2C + 4H \longrightarrow C_2H_4$$

$$2H \longrightarrow H_2.$$

This would, however, involve a tremendous momentary concentration of energy in the molecule. The free radical split

$$C_2H_6 \longrightarrow 2CH_3$$

will be much less endothermic, but will still involve the expenditure of more energy, temporarily, than the direct molecular rearrangement.

The whole problem is analogous to a decision as to whether one should get from one point to another on opposite sides of a mountain by climbing it or detouring it. If the mountain is high and the detour is short, almost everyone will detour. If the mountain is low and the detour long, almost everyone will climb. There is, however, another point in favour of the free radical split. If the chain length is large, a relatively small number of radicals can produce a large amount of decomposition. Hence even if a free radical split is a relatively rare event, the free radical reaction can swamp out the direct molecular reaction if the chains are long enough. If, however, the chains are short, the free radical mechanism can only be of importance if the energy requirements for the bond split are not much greater than those for the rearrangement.

There must also be a "termination" reaction in which the chain-carriers are sometimes lost, as otherwise the chains would be of indefinite length, and one radical introduced into ethane would cause the decomposition of all of it. The termination reaction postulated by Rice is (5).

$$H + C_2H_5 \rightarrow C_2H_6 \quad \ldots \quad \ldots \quad \ldots \quad (5)$$

Others are possible and we will return to this point.

It should also be noted that if the chains are long, since reaction (2) only occurs once per chain, the formation of $CH_4$ will be negligible. (Actually a small amount of $CH_4$ *is* formed in the reaction). The mechanism thus leads to the correct products, and at least qualitatively this is true in a large number of cases.

If the theory is to be accepted, however, it must account not only for the products of organic decompositions but also for the kinetics of such processes. It is an experimental fact that a large number of organic decompositions follow, at least approximately, a first-order rate law, and it is therefore necessary for the theory to answer two questions: (*a*) If the measured process is really the summation of a complex series of reaction steps, how is it that the overall reaction follows a first-order rate law? (*b*) If, as is postulated, most reactions occur by breaking of a C—C bond, how is it that experimental activation energies for decomposition reactions are usually far smaller than the dissociation energy of this bond?

Rice and Herzfeld answered these questions by showing that mechanisms could be devised on a free radical basis which would lead to a first-order rate. Further, by a suitable choice of the activation energies of the part reactions, the apparent activation energy of the overall reaction could be made to agree with the experimental value.

Thus it can be shown by a so-called steady state treatment of the above mechanism for the ethane decomposition, with certain reasonable approximations, that

$$\left(\frac{-d}{dt}\right)[C_2H_6] = \left(\frac{k_1k_3k_4}{k_5}\right)^{\frac{1}{2}}[C_2H_6].$$

Hence the overall reaction is first-order. Also

$$E_{\text{overall}} = \tfrac{1}{2}(E_1 + E_3 + E_4 - E_5)$$
$$= 66.3 \text{ kcal.},$$

which is considerably less than $E_1$. It should be emphasized, however, that this result is dependent on the choice of (5) as the chain-ending step. The choice of one or other of the possible chain-ending steps : $CH_3 + CH_3$, $C_2H_5 + C_2H_5$, $H + CH_3$, etc., would yield a different activation energy.

It should also be emphasized that the choice of the chain-ending step cannot be made in an entirely arbitrary way. Depending on the activation energies, $E_2$, $E_3$ and $E_4$, the relative values of $[H]$, $[CH_3]$ and $[C_2H_5]$ will vary enormously, and these will govern the relative importance of the possible chain-ending steps. For a complete mechanism, all possible chain-ending steps should obviously be included, but this complicates the mathematics so that the situation cannot be handled. Any mechanism which employs only one chain-ending step is therefore to be regarded as an approximation which can only be expected to hold over a limited range of experimental conditions.

Free radical mechanisms of this sort are of course highly speculative and could hardly have been taken seriously in the absence of other evidence. Striking support for the fundamental idea of free-radical chain reactions was, however, immediately forthcoming. Various workers showed that it was possible to start chains in a number of decompositions at temperatures below the normal decomposition range by adding radicals (produced by the decomposition of other substances thermally or photochemically). Thus butane can be "sensitized" by the presence of decomposing tetramethyl lead :

$$CH_3 + C_4H_{10} \longrightarrow CH_4 + C_4H_9 \text{ etc.}$$

These observations prove that free radicals can cause chain decomposition of a large number of organic substances. They do not, however, necessarily prove that such free-radical chain decomposition occurs in the normal pyrolysis of the substances concerned.

Further evidence for the chain character of a large number of decomposition reactions is furnished by the nitric oxide inhibition method. This employs nitric oxide as a radical trap, *i.e* ,

$$R + NO \longrightarrow RNO.$$

Radicals are thus removed from the system and chains are prevented.

On the assupmtion that maximum inhibition by nitric oxide corresponds to the complete suppression of chains normally present, chain lengths of from two to twenty may be calculated for the decomposition of a number of substances. This is a definite evidence for the presence of chains, but in most cases the chain lengths thus obtained are far too small to be in accord with the Rice mechanisms. In some cases it seems probable that the Rice mechanism may hold for a fraction of the total reaction, the remainder of the substance decomposing by a molecular mechanism. There is also some doubt if the maximum inhibition produced by increasing amounts of nitric oxide really corresponds to the complete suppression of chain processes.

The difficulties in the interpretation of inhibition mechanisms emphasize the impossibility of obtaining a yes-or-no answer to the question of the applicability of the Rice mechanisms. Particularly in the last 10 years it has been apparent that what is mainly required is not the investigation of mechanisms of decomposition of individual substances, but rather the independent investigation of the rates of reactions involving organic free radicals. If the rates of such reactions could be determined unambiguously, it would be possible to make many detailed predictions about the overall mechanisms of organic reactions.

As a result, the mechanisms of thermal reactions have ceased to be of major interest as far as gas phase free-radical chemistry is concerned. Attention has been concentrated rather on individual free-radical reactions, and these are usually best investigated by photochemical means. Already such investigations have shown that, while the Rice mechanisms are surprisingly correct in principle, they are grossly over-simplified in practice. Decomposition mechanisms are thus much more complicated than what had been assumed. For the rest of this lecture we will, therefore, not consider further the mechanisms of thermal decompositions, but will discuss the kinetics of radical reactions in the gas phase.

The direct investigation of free-radical reactions is a matter of some difficulty. The first requirement is of course a supply of radicals. In dealing with the reactions of stable substances the investigation is commenced by mixing known quantities of the purified substances. In the case of radicals with a life of $10^{-3}$ to $10^{-6}$ secs., this is of course impossible and radicals can only be obtained by preparing them *in situ* and allowing them to react immediately with whatever substance is in their neighbourhood. As a result, there are in the first place some uncertainties as to whether radicals are present at all and as to which radicals may be there. In the second place, at any given time there will normally be relatively few radicals present. This difficulty is overcome in flash photolysis where very high radical concentrations are obtained. However, flash photolysis experiments are rarely possible under isothermal conditions and therefore often involve great uncertainties in interpretation. Thirdly, since radicals are prepared *in situ* they always exist in the presence of a very large amount of foreign material, *i.e.*, the material from which they are formed. Thus if the methyl radical is prepared by the photolysis of acetone, we may have, say, 50 mm of acetone and $10^{-5}$ mm or less of methyl. A fourth problem is that analysis is very difficult because of the short life of the radicals and any analytical

method which is used, is apt to produce a drastic disturbance in the system. As a result, the amount and nature of the radicals have often to be inferred from the amount of some stable substance formed and the assumption of the mechanism by which it arises. In general, what has to be done is to draw up a mechanism consisting of several plausible stages, deduce mathematically its significance as far as the final products are concerned, and the effect on the rate of the various experimental parameters, and then determine if the mechanism fits the experimental results. In this way it is possible gradually to build up a knowledge of these reactions and slowly and painfully to establish a set of self-consistent data on the rates of free-radical reactions.

The experimental problem is fundamentally the following. For a reaction of the type $CH_3 + RH \rightarrow CH_4 + R$ one can determine the rate of reaction by measuring the rate of formation of methane. We thus have the expression for the rate constant of the reaction

$$R_{CH_4} = k\,[CH_3]\,[RH],$$

where $R_{CH_4}$ is the rate of formation of methane, and $[CH_3]$ and $[RH]$ are the concentrations of $CH_3$ and RH respectively. However, since $[CH_3]$ is normally unknown it is impossible to calculate $k$. The whole problem of the investigation of radical reactions is to get around this difficulty. In the past, two methods were employed. In the first place, provided that the whole mechanism of the reaction and all its steps are known in detail, it will be possible to calculate the concentration of methyl from the mechanism. This method has often been followed but has often led to erroneous conclusions. Its great weakness is that the mechanism must be known in complete detail, and any missing step may entirely upset the calculations. The second method which has produced much useful data has been to investigate reactions in such a way that methyl radical concentrations can be cancelled in equations involving two reactions, and thus relative rate constants may be obtained in a comparatively simple manner. Finally, in recent years it has become possible to arrive at values of methyl radical concentrations from a knowledge of the rate of the methyl radical recombination, and this has enabled much accurate and reliable data to be accumulated in the last five years.

As an example of the problem, and of the kind of method which may be used, let us consider the investigation of hydrogen abstraction by methyl radicals, as in the above case. The necessary methyl radicals may be produced by the photolysis of acetone. At high temperatures the pertinent steps in the mechanism of the reaction can be written as:

$$CH_3COCH_3 \rightarrow 2CH_3 + CO \qquad \ldots\ (1)$$

$$CH_3 + CH_3COCH_3 \rightarrow CH_4 + CH_2COCH_3 \qquad \ldots\ (2)$$

$$2CH_3 \rightarrow C_2H_6. \qquad \ldots\ (3)$$

For the rates of reactions (2) and (3) we can write

$$R_{CH_4} = k_2[CH_3]\,[\text{acetone}]$$

$$R_{C_2H_6} = k_3[CH_3]^2$$

$$\frac{R_{CH_4}}{R_{C_2H_6}^{\frac{1}{2}}} = \frac{k_2\,[\text{acetone}]}{k_3^{\frac{1}{2}}}.$$

We can thus get a measure of the relative rates of (2) and (3), *i.e.*, the ratio $k_2/k_3^{\frac{1}{2}}$.

In the presence of a hydrocarbon, methane will also be formed by

$$CH_3 + RH \longrightarrow CH_4 + R \qquad \ldots (4)$$

and we have

$$R_{CH_4} = k_2[CH_3]\,[\text{acetone}] + k_4[CH_3]\,[RH]$$
$$R_{C_2H_6} = k_3[CH_3]^2$$
$$\frac{R_{CH_4}}{R_{C_2H_6}^{\frac{1}{2}}} = \frac{k_2\,[\text{acetone}] + k_4\,[RH]}{k_3^{\frac{1}{2}}}$$

We can thus get information on the relative rates of various reactions of type (4), referred to the rate of combination of methyl radicals. In somewhat similar ways a variety of free radical reactions have been investigated in recent years, and we now know a great deal more about the rates of such "elementary reactions", and about the dissociation energies of bonds in organic molecules.

In reporting the results of such experiments it is customary to do so in terms of the Arrhenius equation

$$k = Ae^{-E/RT},$$

where $k$ is the rate constant of the reaction, $A$ is a constant, called the frequency factor, and $E$ is the activation energy. It should be emphasized that the quantities $A$ and $E$ must both be determined experimentally, and that assumptions that $A$ has always the same value for unimolecular or bimolecular reactions have no foundation, either experimental or theoretical. It is sometimes convenient to write

$$A = PZ$$

where $Z$ is the collision number (assuming gas-kinetic cross-sections) and $P$ is the so-called "steric factor". It may be objected that the calculation of $P$ involves unjustifiable assumptions about the collision cross-section. It should be emphasized, however, that the fundamental question is whether $A$ is low or high, and that $P$ is merely a conventional method of expressing this. An unusually low value of $P$, for example, implies an unusually low value of $A$ irrespective of any uncertainties about collision cross-sections.

Results of particular interest have been obtained for two types of reaction. The first of these involves radical-radical interactions, e.g.

$$2C_2H_5 \longrightarrow C_4H_{10} \qquad \text{recombination}$$
$$\text{or} \quad \longrightarrow C_2H_4 + C_2H_6 \qquad \text{disproportionation.}$$

A number of determinations have been made of radical recombinations for $CH_3$, $C_2H_5$ and $CF_3$. These indicate values of the frequency factor at higher pressures of the order of $2 \times 10^{13}$ c.c. mole$^{-1}$ sec.$^{-1}$, corresponding to collision efficiencies of the order of unity, *i.e.*, to an activation energy of zero and a steric factor of about unity. Such measurements are very important since they furnish a "yard-stick" for the values of the concentration of $CH_3$, $C_2H_5$ or $CF_3$ in many reaction systems.

A second type of reaction for which much information has been obtained is hydrogen-abstraction such as (4). As pointed out above, relative values of $k_4$ have been obtained in the past. Now that the rate of recombination of methyl radicals

is known, the values of $k_4$ become absolute. In recent years accurate data for about 100 reactions of this type have been obtained. The main points of interest are, first, that the influence of chemical structure on the reaction rate is in good agreement with predictions from organic chemistry, tertiary hydrogen atoms being more reactive than secondary, which in turn are more reactive than primary. Secondly, activation energy values are found to cover a relatively narrow range (mainly from 6–13 kcal.). Finally, the most striking feature of the results is that it has been established unequivocally that the frequency factors for these reactions are relatively low, in the range from $10^9$ to $10^{11}$ c.c. mole$^{-1}$ sec.$^{-1}$ (*i.e.* the steric factors are in the range from $10^{-4}$ to $10^{-2}$). Recent theoretical investigations by Bywater, Stepukhovich and others indicate that theory is sufficiently elastic to cover this range of values without fundamental modification.

Considerable information has also been obtained on other types of radical reaction and it is now possible, therefore, to make much more accurate assignments of activation energies and frequency factors to the part-reactions in radical mechanisms of the Rice type. Thus if we consider the ethane decomposition once more, we can make a fairly accurate assignment of activation energies. However, the mechanism turns out to be still in difficulties and it appears to be unlikely that the entire process proceeds by a radical mechanism, but certainly, that part of it does.

The above difficulties with the mechanism of the ethane decomposition raise the question of the status of all the Rice mechanisms. A wide variety of evidence indicates that these mechanisms contain much basic truth. There is no doubt that free radicals *are* produced in most gas-phase decompositions. There is also no doubt that the types of reaction postulated in these mechanisms are inherently plausible, and occur readily. There are, however, many reasons why the mechanisms cannot be expected to be quantitatively true in all cases.

(*a*). The main trouble is that a very large number of part-reactions are possible. The mechanisms essentially choose certain of these and neglect the others. It seems certain that in most cases the mechanism must vary with temperature and pressure if conditions are varied over a wide enough range.

(*b*). From one decomposition to another, there will be small but significant changes in the rates and activation energies of the various types of reaction. These will profoundly alter the relative rates of the part-reactions, the concentrations of radicals, etc. As a result one must expect wide difference with different substances.

(*c*). In particular it is to be expected that the participation of non-free radical processes will vary widely in importance from case to case.

As a result, it appears that the search for a universal type of mechanism for decomposition reactions is probably ill-advised, and various substances may be expected to exhibit their own idiosyncracies. There is, however, no doubt of the importance of free-radical mechanisms, or of their at least partial applicability to most substances. In the meantime the sorting out of the complications is a matter which requires a great deal of further experiment; and an empirical chemistry of short-lived substances must be built up.

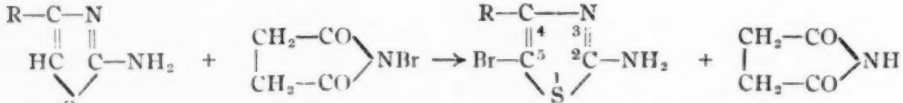
[Jour. Indian Chem. Soc., Vol. 36, No. 5, 1959]

# SHORT NOTES

## BROMINATION OF 2-AMINOTHIAZOLES WITH THE HELP OF *N*-BROMOSUCCINIMIDE

By G. N. Mahapatra

In the present communication, each of the seventeen 2-amino-4-arylthiazoles, synthesised and brominated earlier with liquid bromine in acetic acid at 0° (Mahapatra, this *Journal*, 1956, **33**, 527), has been brominated with the help of *N*-bromosuccinimide at the room temperature in chloroform medium, giving rise to the corresponding 5-bromo-4-aryl-2-aminothiazole in each case. *N*-Bromosuccinimide being a good brominating agent, brominates the 2-aminothiazoles without affecting the free amino group, provided that it is not in excess and is added very slowly. If *N*-bromosuccinimide is in excess of the requisite amount, or added too quickly, side reaction takes place and the mixture gradually becomes dark and a resinous product is ultimately isolated. This shows that *N*-bromosuccinimide attacks the free amino group only when it is in excess, and this makes the compound gummy. To avoid such side reactions, the free amino group may be protected by acetylation and the acetylated aminothiazole can be brominated with the help of *N*-bromosuccinimide without having any side reaction, even though the latter is in excess.



4-Aryl-2 aminothiazole. *N*-Bromosuccinimide. 4-Aryl-5 bromo-2-aminothiazole.

The position of the bromine atom in the thiazole nucleus is at the carbon atom 5, the evidence for which has already been discussed in an earlier paper (Mahapatra, *loc. cit.*). The yields in these cases are generally higher than those obtained from direct bromination, and the process is much simpler.

*Bromination* of *2-Amino-4-phenylthiazole*.—2-Amino-4-phenylthiazole (1 g) was dissolved in chloroform (40 c.c.) and the mixture was mechanically stirred at the room temperature. *N*-Bromosuccinimide (1 g.), dissolved in chloroform (30 c.c.), was added gradually during 20 minutes with stirring. After the addition was complete, the stirring was continued for 15 minutes and then the chloroform was distilled off in vacuum. The solid residue was treated with concentrated ammonia, filtered and washed. The product was finally crystallised from alcohol, m.p. 108°, yield 80%. (Found : Br, 30.97 ; S, 12.21. Calc. for $C_9H_7N_2BrS$ : Br, 31.37 ; S, 12.55%).

All the remaining 2-amino-4-arylthiazoles were brominated by *N*-bromosuccinimide in the same way as shown above and yielded the corresponding 5-bromo derivative in each case.

The author is highly grateful to the Government of India, Ministry of Scientific Research and Cultural Affairs, for a research grant to carry out the above work.

Mayurbhanj Chemical Laboratory,
Ravenshaw College, Cuttack.

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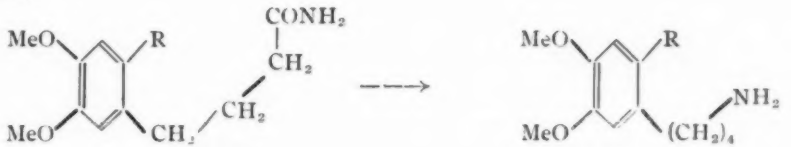
# SYNTHESIS OF δ-(2-ALKYL-4 : 5-DIMETHOXYPHENYL)-*n*-BUTYLAMINES

By H. N. Sharma and C. N. Kachru

β-(2-Alkyl-4 : 5-dimethoxyphenyl) ethylamines were prepared by Kachru and Pathak (this *Journal*, 1957, **34**, 611) and their *in vitro* amoebacidal activity was studied by Kaushiva (*J. Sci. Ind. Res.*, 1957, **16C**, 224) who pointed out that hexyl substitution conferred maximum activity. Moreover, the β compounds seemed to show greater activity than the corresponding α-compounds. Based on these observations, the preparation of γ-(2-alkyl 4 : 5-dimethoxyphenyl)-propylamines and δ-(2-alkyl-4 : 5-dimethoxyphenyl)-*n*-butylamines was taken up. The synthesis of the former ones has been described by Sharma and Kachru (this *Journal*, 1959, **36**, 117), while that of the latter ones is described here. These would be tested for amoebacidal activity.




(I) (II)

γ-(2-Alkyl-4 : 5-dimethoxyphenyl)-*n*-butyramides (I) were prepared as intermediates in the course of the synthesis of γ-(2-alkyl-4 : 5-dimethoxyphenyl)-propylamines (Sharma and Kachru, *loc. cit.*). These amides (I) were reduced to the corresponding amines (II) with $LiAlH_4$ in very low yields.

*Reduction of the Amides with* $LiAlH_4$.—In a 500 c.c. two-necked flask, fitted with a reflux condenser and a guard-tube, were placed dry ether (200 c.c.) and $LiAlH_4$ (0.015 *M*) and the mixture was refluxed for about 10 minutes, cooled and the γ-alkyl- *n*-butyramide (0.01 *M*), dissolved in dry ether, was added to the slurry at such a rate that a steady gentle refluxing was maintained. After the addition was complete (1 hour), it was refluxed for 8 hours and the excess of $LiAlH_4$ then decomposed by the dropwise addition of water. The ethereal layer was decanted and the residue extracted with fresh ether. The combined ether extract was dried over KOH. Ether was removed and the residual amine isolated either as a picrate or as a hydrochloride.

TABLE I

δ-(2-Alkyl-4 : 5-dimethoxyphenyl)-*n*-butylamine (II).

| Alkyl. | Cryst. from. | M.P. | Formula. | % Nitrogen. | |
|---|---|---|---|---|---|
| | | | | Found. | Calc. |
| | Picrates. | | | | |
| Me | EtOH (dil.) | 164-65° | $C_{19}H_{24}O_9N_4$ | 12.27 | 12.39 |
| Et | Do | 176° | $C_{20}H_{26}O_9N_4$ | 12.02 | 12.02 |
| Pr$^n$ | Do | 187° | ... | ... | ... |
| Bu$^n$ | EtOH | 175° | ... | ... | ... |
| | Hydrochlorides. | | | | |
| Pr$^n$ | EtAc + EtOH (abs.) | 155° | $C_{15}H_{26}O_2NCl$ | 4.75 | 4.87 |
| Bu$^n$ | EtAc | 128° | $C_{16}H_{28}O_2NCl$ | 4.72 | 4.64 |

The authors express their sincere thanks to Dr. Mata Prasad, Vice-Chancellor, Vikram University, for facilities during the course of the investigation.

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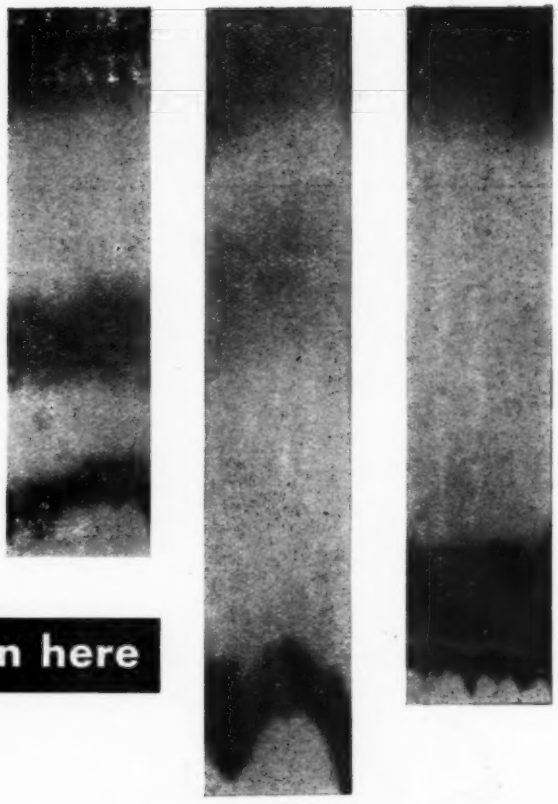

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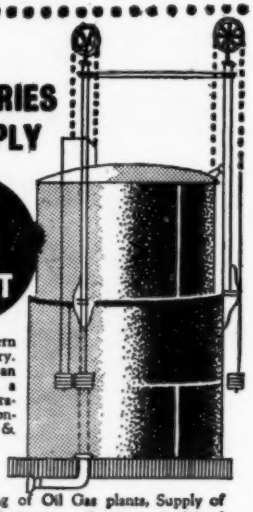

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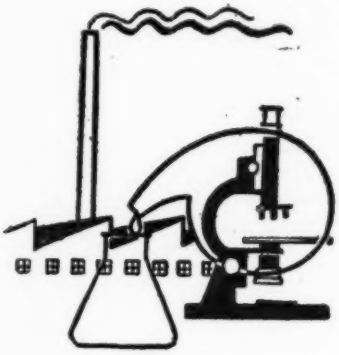

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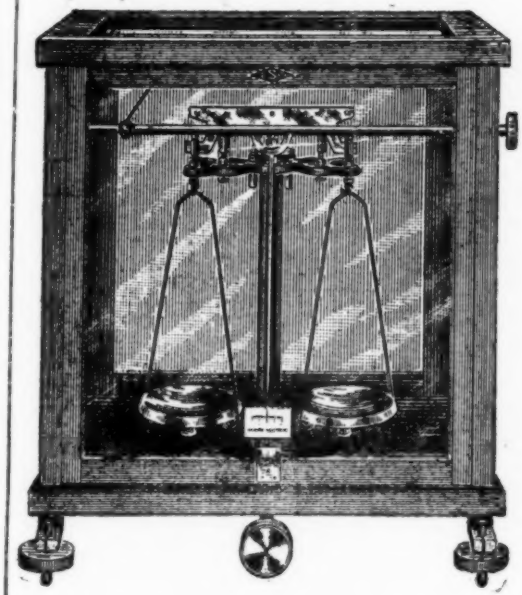

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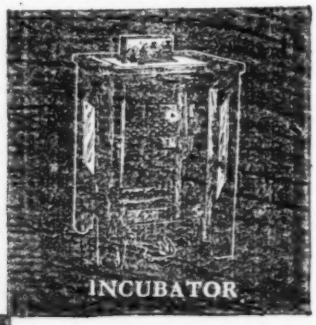

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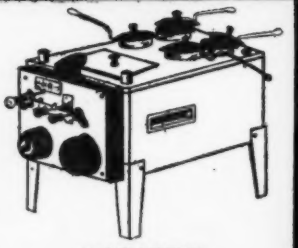

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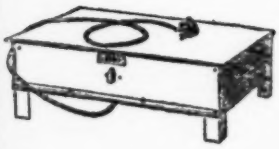

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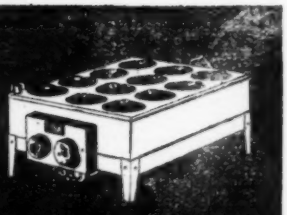

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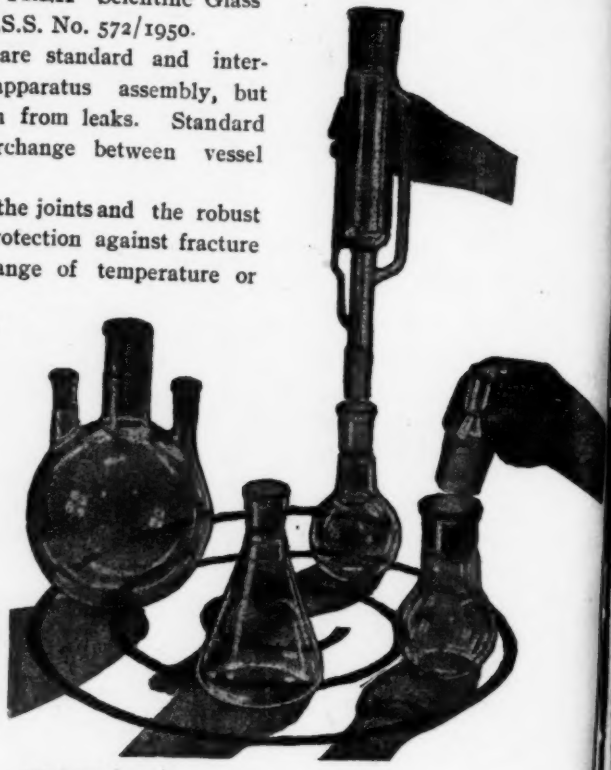

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